PCT/IB 05 / 00510
(24.02.05)

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PCT/IB05/00510

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

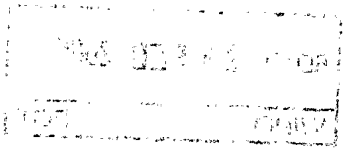
In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Signed William Morell

Dated 19 January 2005



Patents Form 1/77

Patents Act 1977
(Rule 16)

09MAR04 E879255-1 D01298
P01/7700 0.00-0405200.7 NONE

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

0 8 MAR 2004

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

PC26135

2. Patent application number
(The Patent Office will fill in this part)

0405200.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

Patents ADP number *(if you know it)*

6892673001

United Kingdom

If the applicant is a corporate body, give the country/state of its incorporation

THE PATENT OFFICE
SN
- 8 MAR 2004
LONDON

4. Title of the invention

COMBINATIONS COMPRISING ALPHA-2-DELTA LIGANDS

5. Name of your agent *(if you have one)*

Mrs. E. Dolan

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

European Pharma Patent Department
Pfizer Limited,
Ramsgate Road,
Sandwich, Kent,
CT13 9NJ
United Kingdom

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	67
Claim *(s)*	2
Abstract	1
Drawing *(s)*	0

SN

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature E. Dolan Date 08 March 2004

12. Name and daytime telephone number of person to contact in the United Kingdom — Mrs. E. Dolan 01304.645135

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered Yes Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

f) *For details of the fee and ways to pay please contact the Patent Office.*

COMBINATIONS COMPRISING ALPHA-2-DELTA LIGANDS

FIELD OF THE INVENTION

This invention relates to a combination of an alpha-2-delta ligand and an atypical antipsychotic. The invention further relates to a combination of an alpha-2-delta ligand and an atypical antipsychotic for the treatment of pain. It also relates to a method for treating pain through the use of effective amounts of a combination of an alpha-2-delta ligand and an atypical antipsychotic. The invention further relates to a synergistic combination of an alpha-2-delta ligand and an atypical antipsychotic and the use of such for the treatment of pain.

BACKGROUND TO THE INVENTION

An alpha-2-delta receptor ligand is any molecule which binds to any sub-type of the human calcium channel alpha-2-delta sub-unit. The calcium channel alpha-2-delta sub-unit comprises a number of receptor sub-types which have been described in the literature:

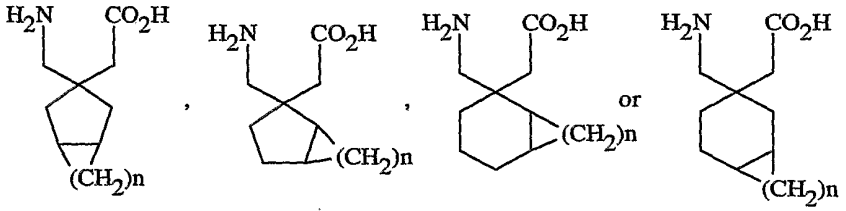
e.g. N. S. Gee, J. P. Brown, V. U. Dissanayake, J. Offord, R. Thurlow, and G. N. Woodruff, *J-Biol-Chem* 271 (10):5768-76, 1996, (type 1); Gong, J. Hang, W. Kohler, Z. Li, and T-Z. Su, *J.Membr.Biol.* 184 (1):35-43, 2001, (types 2 and 3); E. Marais, N. Klugbauer, and F. Hofmann, *Mol.Pharmacol.* 59 (5):1243-1248, 2001. (types 2 and 3); and N. Qin, S. Yagel, M. L. Momplaisir, E. E. Codd, and M. R. D'Andrea. *Mol.Pharmacol.* 62 (3):485-496, 2002, (type 4). They may also be known as GABA analogs.

Alpha-2-delta ligands have been described for the treatment of a number of indications. The best known alpha-2-delta ligand, gabapentin (Neurontin®), 1-(aminomethyl)-cyclohexylacetic acid, was first described in the patent literature in the patent family comprising US4024175. The compound is approved for the treatment of epilepsy and neuropathic pain.

A second alpha-2-delta ligand, pregabalin, (S)-(+)-4-amino-3-(2-methylpropyl)butanoic acid, is described in European patent application publication number EP641330 as an anti-convulsant treatment useful in the treatment of epilepsy and in EP0934061 for the treatment of pain.

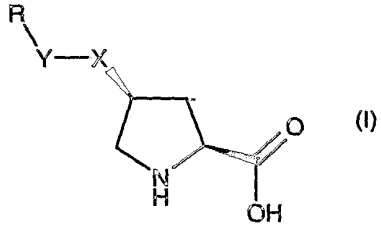
Further alpha-2-delta ligands are described in the following documents.

International Patent Application Publication No. WO0128978, describes a series of novel bicyclic amino acids, their pharmaceutically acceptable salts, and their prodrugs of formula:



wherein n is an integer of from 1 to 4, where there are stereocentres, each center may be independently R or S, preferred compounds being those of Formulae I-IV above in which n is an integer of from 2 to 4.

International Patent Application No. PCT/IB03/04697 (unpublished at the filing date of the present invention) describes compounds of the formula (I), below;



(I)

wherein

either X is O, S, NH or CH_2 and Y is CH_2 or a direct bond, or Y is O, S or NH and X is CH_2; and

R is a 3-12 membered cycloalkyl, 4-12 membered heterocycloalkyl, aryl or heteroaryl, wherein any ring may be optionally substituted with one or more substituents independently selected from

halogen, hydroxy, cyano, nitro, amino, hydroxycarbonyl,
C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl,
C_1-C_6 alkoxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkyl, perfluoro C_1-C_6 alkyl,
perfluoroC_1-C_6 alkoxy,
C_1-C_6 alkylamino, di- C_1-C_6 alkylamino, aminoC_1-C_6 alkyl, C_1-C_6 alkylaminoC_1-C_6 alkyl,
di-C_1-C_6 alkylaminoC_1-C_6 alkyl,
C_1-C_6acyl, C_1-C_6acyloxy, C_1-C_6acyloxyC_1-C_6 alkyl, C_1-C_6 acylamino,
C_1-C_6 alkylthio, C_1-C_6 alkylthiocarbonyl, C_1-C_6 alkylthioxo, C_1-C_6 alkoxycarbonyl,
C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfonylamino,
aminosulfonyl, C_1-C_6 alkylaminosulfonyl, di-C_1-C_6 alkylaminosulfonyl,
3-8 membered cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and monocyclic heteroaryl;
or a pharmaceutically acceptable salt thereof.

Conventional antipsychotics are antagonists of dopamine (D_2) receptors. The atypical antipsychotics also have D_2 antagonistic properties but possess different binding kinetics to these receptors and activity at other receptors, particularly 5-HT_{2A}, 5-HT_{2C} and 5-HT_{2D} (Schmidt B *et al*, Soc. Neurosci. Abstr. 24:2177, 1998).

The class of atypical antipsychotics includes clozapine (clozaril®), 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (US Patent No. 3,539,573); risperidone (risperdal®), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one (US Patent No. 4,804,663); olanzapine (zyprexa®), 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (US Patent No. 5,229,382); quetiapine (seroquel®), 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol (US Patent No. 4,879,288); aripiprazole (abilify®), 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro carbostyril and 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro-2(1H)-quinolinone (US Patent Nos. 4,734,416 and 5,006,528); sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one (US Patent No. 4,710,500); amisulpride (US Patent No. 4,410,822); ziprasidone (geodon®), 5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-3-yl]ethyl]-6-chloroindolin-2-one hydrochloride hydrate

(US Patent No. 4,831,031); and asenapine, trans-5-Chloro-2,3,3a,12b-tetrahydro-2-methyl-1H- dibenz [2,3:6,7] oxepino [4,5-c] pyrrole maleate.

The contents of all patents and publications cited within the present application are hereby incorporated by reference.

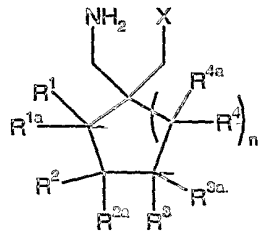
SUMMARY OF THE INVENTION

It has now been found that combination therapy with an alpha-2-delta ligand and an atypical antipsychotic results in improvement in the treatment of pain. Furthermore, when administered simultaneously, sequentially or separately, the alpha-2-delta ligand and atypical antipsychotic may interact in a synergistic manner to control pain. This synergy allows a reduction in the dose required of each compound, leading to a reduction in the side effects and enhancement of the clinical utility of the compounds.

Accordingly, the invention provides, as a first aspect, a combination product comprising an alpha-2-delta ligand and an atypical antipsychotic.

As an alternative or further aspect, the invention provides a synergistic combination product comprising an alpha-2-delta ligand and an atypical antipsychotic.

Useful cyclic alpha-2-delta ligands of the present invention are illustrated by the following formula (I):



(I)

wherein X is a carboxylic acid or carboxylic acid bioisostere;

n is 0, 1 or 2; and

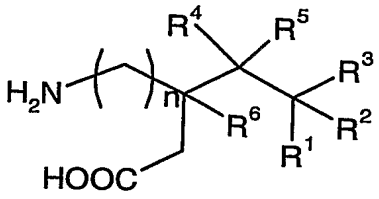
R^1, R^{1a}, R^2, R^{2a}, R^3, R^{3a}, R^4 and R^{4a} are independently selected from H and C_1-C_6 alkyl, or

R^1 and R^2 or R^2 and R^3 are taken together to form a C_3-C_7 cycloalkyl ring, which is optionally substituted with one or two substituents selected from C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof.

In formula (I), suitably, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 are independently selected from H and methyl, or R^{1a}, R^{2a}, R^{3a} and R^{4a} are H and R^1 and R^2 or R^2 and R^3 are taken together to form a C_3-C_7 cycloalkyl ring, which is optionally substituted with one or two methyl substituents. A suitable carboxylic acid bioisostere is selected from tetrazolyl and oxadiazolonyl. X is preferably a carboxylic acid.

In formula (I), preferably, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 are independently selected from H and methyl, or R^{1a}, R^{2a}, R^{3a} and R^{4a} are H and R^1 and R^2 or R^2 and R^3 are taken together to form a C_4-C_5 cycloalkyl ring, or, when n is 0, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 form a cyclopentyl ring, or, when n is 1, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 are both methyl or R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 form a cyclobutyl ring, or, when n is 2, R^1, R^{1a}, R^2, R^{2a}, R^3, R^{3a}, R^4 and R^{4a} are H, or, n is 0, R^1, R^{1a}, R^{2a}, R^{3a}, R^4 and R^{4a} are H and R^2 and R^3 form a cyclopentyl ring.

Useful acyclic alpha-2-delta ligands of the present invention are illustrated by the following formula (II):



(II)

wherein:

n is 0 or 1, R^1 is hydrogen or (C_1-C_6)alkyl; R^2 is hydrogen or (C_1-C_6)alkyl; R^3 is hydrogen or (C_1-C_6)alkyl; R^4 is hydrogen or (C_1-C_6)alkyl; R^5 is hydrogen or (C_1-C_6)alkyl and R^2 is hydrogen or (C_1-C_6)alkyl, or a pharmaceutically acceptable salt thereof.

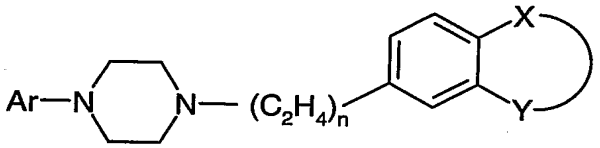
According to formula (II), suitably R^1 is C_1-C_6 alkyl, R^2 is methyl, R^3 – R^6 are hydrogen and n is 0 or 1. More suitably R^1 is methyl, ethyl, n-propyl or n-butyl, R^2 is methyl, R^3 – R^6 are hydrogen and n is 0 or 1. When R^2 is methyl, R^3 – R^6 are hydrogen and n is 0, R^1 is suitably ethyl, n-propyl or n-butyl. When R^2 is methyl, R^3 – R^6 are hydrogen and n is 1, R^1 is suitably methyl or n-propyl. Compounds of formula (II) are suitably in the 3S,5R configuration.

Examples of alpha-2-delta ligands for use with the present invention are those compounds generally or specifically disclosed in US4024175, particularly gabapentin, EP641330, particularly pregabalin, US5563175, WO9733858, WO9733859, WO9931057, WO9931074, WO9729101, WO02085839, particularly [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, WO9931075, particularly 3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one and C-[1-(1H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, WO9921824, particularly (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, WO0190052, WO0128978, particularly (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, EP0641330, WO9817627, WO0076958, particularly (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, PCT/IB03/00976, particularly (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-Amino-5-methyl-octanoic acid, PCT/IB03/04697, particularly (2*S*,4*S*)-4-(3-fluoro-phenoxymethyl)-pyrrolidine-2-carboxylic acid, (2*S*,4*S*)-4-(2,3-difluoro-benzyl)-pyrrolidine-2-carboxylic acid, (2*S*,4*S*)-4-(3-chlorophenoxy)proline and (2*S*,4*S*)-4-(3-fluorobenzyl)proline, EP1178034, EP1201240, WO9931074, WO03000642, WO0222568, WO0230871, WO0230881, WO02100392, WO02100347, WO0242414, WO0232736 and WO0228881 or pharmaceutically acceptable salts thereof, all of which are incorporated herein by reference.

Preferred alpha-2-delta ligands of the present invention include: gabapentin, pregabalin, [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-Aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-Amino-

5-methyl-octanoic acid, (2*S*,4*S*)-4-(3-fluoro-phenoxymethyl)-pyrrolidine-2-carboxylic acid, (2*S*,4*S*)-4-(2,3-difluoro-benzyl)-pyrrolidine-2-carboxylic acid, (2*S*,4*S*)-4-(3-chlorophenoxy)proline and (2*S*,4*S*)-4-(3-fluorobenzyl)proline, or pharmaceutically acceptable salts thereof. Particularly preferred alpha-2-delta ligands of the present invention are selected from gabapentin, pregabalin and (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, and (2*S*,4*S*)-4-(3-fluoro-phenoxymethyl)-pyrrolidine-2-carboxylic acid, or pharmaceutically acceptable salts thereof.

Atypical antipsychotics useful according to the present invention include those comprised within the disclosure of US 4,831,031, i.e. the compounds of formula (I):



(I)

wherein Ar is naphthyl optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; quinolyl; isoquinolyl; 6-hydroxy-8-quinolyl; benzoisothiazolyl or an oxide or dioxide thereof each optioannly substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; benzothiazolyl; benzothiadiazolyl; benzotriazolyl; benzoxazolyl; benzoxazolonyl; indolyl; indanyl optionally substituted by one or two fluoro; 3-indazolyl optionally substituted by 1-trifluoromethylphenyl; or phthalazinyl;

n is 1 or 2; and

X and Y together with the phenyl to which they are attached form quinolyl; 2-hydroxyquinolyl; benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 3-hydroxyindazolyl; indolyl; spiro[cyclopentane-1,3'-indolinyl]; oxindolyl optionally substituted by one to three of (C_1-C_3)alkyl, or one of chloro, fluoro or phenyl, said phenyl being optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolinyl; benzothiazolonyl; benzoimidazolonyl; or benzotriazolyl.

A particular preferred compound of formula (I) is ziprasidone.

Examples of atypical antipsychotics for use in the present invention are the compounds generically and specifically disclosed in US 4,831,301, particularly ziprasidone, US 5,229,382, particularly olanzapine, US 3,539,573, particularly clozapine,

US 4,804,663, particularly risperidone, US 4,710,500, particularly sertindole, US 4,879,288, particularly quetiapine, US 4,734,416, particularly aripiprazole, and US 4,401,822, particularly amisulpride, and asenapine, or pharmaceutically acceptable salts thereof, all of which are incorporated herein by reference.

Suitable atypical antipsychotics for use in the present invention include ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, asenapine and amisulpride or pharmaceutically acceptable salts thereof. Preferably the atypical antipsychotic is ziprasidone, or a pharmaceutically acceptable salt thereof.

The suitability of any particular atypical antipsychotic can be readily determined by evaluation of its potency and selectivity using literature methods followed by evaluation of its toxicity, absorption, metabolism, pharmacokinetics, etc in accordance with standard pharmaceutical practices.

As an alternative or further aspect of the present invention, there is provided a combination comprising gabapentin, or a pharmaceutically acceptable salt thereof, and an atypical antipsychotic selected from ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, asenapine and amisulpride, or a pharmaceutically acceptable salt thereof. A particularly preferred combination comprises gabapentin and ziprasidone, and their pharmaceutically acceptable salts.

As an alternative or further aspect of the present invention, there is provided a combination comprising pregabalin and an atypical antipsychotic selected from ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, asenapine and amisulpride, and their pharmaceutically acceptable salts. A particularly preferred combination comprises pregabalin and ziprasidone, and their pharmaceutically acceptable salts.

As an alternative or further aspect of the present invention, there is provided a combination comprising (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid or a pharmaceutically acceptable salt thereof, and an atypical antipsychotic. Suitably, there is provided a combination comprising (1α,3α,5α)(3-aminomethyl-

bicyclo[3.2.0]hept-3-yl)-acetic acid or a pharmaceutically acceptable salt thereof, and an atypical antipsychotic selected from ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, asenapine and amisulpride, or a pharmaceutically acceptable salt thereof. A particularly preferred combination comprises (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and ziprasidone, and their pharmaceutically acceptable salts.

As an alternative or further aspect of the present invention, there is provided a combination comprising (2*S*,4*S*)-4-(3-chlorophenoxy)proline or a pharmaceutically acceptable salt thereof, and an atypical antipsychotic. Suitably, there is provided a combination comprising (2*S*,4*S*)-4-(3-chlorophenoxy)proline or a pharmaceutically acceptable salt thereof, and an atypical antipsychotic selected from ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, asenapine and amisulpride, or a pharmaceutically acceptable salt thereof. A particularly preferred combination comprises (2*S*,4*S*)-4-(3-chlorophenoxy)proline and ziprasidone, and their pharmaceutically acceptable salts.

As an alternative or further aspect of the present invention, there is provided a combination comprising (2*S*,4*S*)-4-(3-fluorobenzyl)proline or a pharmaceutically acceptable salt thereof, and an atypical antipsychotic. Suitably, there is provided a combination comprising (2*S*,4*S*)-4-(3-fluorobenzyl)proline or a pharmaceutically acceptable salt thereof, and an atypical antipsychotic selected from ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, asenapine and amisulpride, or a pharmaceutically acceptable salt thereof. A particularly preferred combination comprises (2*S*,4*S*)-4-(3-fluorobenzyl)proline and ziprasidone, and their pharmaceutically acceptable salts.

As a yet further preferred aspect of the present invention, the combination is selected from:

gabapentin and ziprasidone;

gabapentin and olanzapine;

gabapentin and clozapine;

gabapentin and risperidone;
gabapentin and sertindole;
gabapentin and quetiapine;
gabapentin and aripiprazole;
gabapentin and asenapine;
gabapentin and amisulpride;
pregabalin and ziprasidone;
pregabalin and olanzapine;
pregabalin and clozapine;
pregabalin and risperidone;
pregabalin and sertindole;
pregabalin and quetiapine;
pregabalin and aripiprazole;
pregabalin and asenapine;
pregabalin and amisulpride;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and ziprasidone;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and olanzapine;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and clozapine;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and risperidone;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and sertindole;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and quetiapine;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and aripiprazole;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and asenapine;
[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid and amisulpride;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and ziprasidone;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and olanzapine;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and clozapine;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and risperidone;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and sertindole;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and quetiapine;

(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and aripiprazole;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and asenapine;
(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and amisulpride;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and ziprasidone;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and olanzapine;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and clozapine;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and risperidone;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and sertindole;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and quetiapine;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and aripiprazole;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and asenapine;
(3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid and amisulpride;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and ziprasidone;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and olanzapine;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and clozapine;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and risperidone;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and sertindole;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and quetiapine;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and aripiprazole;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and asenapine;
(2*S*,4*S*)-4-(3-chlorophenoxy)proline and amisulpride;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and ziprasidone;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and olanzapine;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and clozapine;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and risperidone;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and sertindole;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and quetiapine;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and aripiprazole;
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and asenapine; and
(2*S*,4*S*)-4-(3-fluorobenzyl)proline and amisulpride;

or pharmaceutically acceptable salts or solvates of either or both components of any such combination.

Particularly preferred combinations of the invention include those in which each variable of the combination is selected from the suitable parameters for each variable. Even more preferable combinations of the invention include those where each variable of the combination is selected from the more suitable, most suitable, preferred or more preferred parameters for each variable.

The combination of the present invention in a single dosage form is suitable for administration to any mammalian subject, preferably human. Administration may be once (o.d.), twice (b.i.d.) or three times (t.i.d.) daily, suitably b.i.d. or t.i.d., more suitably b.i.d, most suitably o.d..

Thus, as a further aspect of the present invention, there is provided the use of a combination, particularly synergistic, of an alpha-2-delta ligand and an atypical antipsychotic in the manufacture of a once, twice or thrice, suitably twice or thrice, more suitably twice, most suitably once daily administration medicament for the curative, prophylactic or palliative treatment of pain.

Determining a synergistic interaction between one or more components, the optimum range for the effect and absolute dose ranges of each component for the effect may be definitively measured by administration of the components over different w/w ratio ranges and doses to patients in need of treatment. For humans, the complexity and cost of carrying out clinical studies on patients renders impractical the use of this form of testing as a primary model for synergy. However, the observation of synergy in one species can be predictive of the effect in other species and animal models exist, as described herein, to measure a synergistic effect and the results of such studies can also be used to predict effective dose and plasma concentration ratio ranges and the absolute doses and plasma concentrations required in other species by the application of pharmacokinetic/pharmacodynamic methods. Established correlations between animal models and effects seen in man suggest that synergy in animals is best-demonstrated using static and dynamic allodynia measurements in rodents that have undergone surgical (e.g. chronic constriction injury) or chemical (e.g. streptozocin) procedures to induce the allodynia. Because of ceiling effects in such models, their value is best assessed in terms of synergistic actions that in neuropathic pain endpoints would correlate to decreasing

advantages. Other models in which existing agents used for the treatment of neuropathic pain give only a partial response are more suited to predict the potential of combinations acting synergistically to produce increased maximal efficacy at maximally tolerated doses of the two components.

Thus, as a further aspect of the present invention, there is provided a synergistic combination for human administration comprising an alpha-2-delta ligand and an atypical antipsychotic, or pharmaceutically acceptable salts or solvates thereof, in a w/w combination range which corresponds to the absolute ranges observed in a non-human animal model, preferably a rat model, primarily used to identify a synergistic interaction. Suitably, the ratio range in humans corresponds to a non-human range selected from between 1:50 to 50:1 parts by weight, 1:50 to 20:1, 1:50 to 10:1, 1:50 to 1:1, 1:20 to 50:1, 1:20 to 20:1, 1:20 to 10:1, 1:20 to 1:1, 1:10 to 50:1, 1:10 to 20:1, 1:10 to 10:1, 1:10 to 1:1, 1:1 to 50:1, 1.1 to 20:1 and 1:1 to 10:1. More suitably, the human range corresponds to a non-human range of 1:10 to 20:1 parts by weight. Preferably, the human range corresponds to a synergistic non-human range of the order of 1:1 to 10:1 parts by weight.

For humans, several experimental pain models may be used in man to demonstrate that agents with proven synergy in animals also have effects in man compatible with that synergy. Examples of human models that may be fit for this purpose include the heat/capsaicin model (Petersen, K.L. & Rowbotham, M.C. (1999) NeuroReport 10, 1511-1516), the i.d capsaicin model (Andersen, O.L., Felsby, S., Nicolaisen, L., Bjerring, P., Jsesn, T.S. & Arendt-Nielsen, L. (1996) Pain 66, 51-62), including the use of repeated capsaicin trauma (Witting, N., Svesson, P., Arendt-Nielsen, L. &Jensen, T.S. (2000) Somatosensory Motor Res. 17, 5-12), and summation or wind-up responses (Curatolo, M. et al. (2000) Anesthesiology 93, 1517 – 1530). With these models, subjective assessment of pain intensity or areas of hyperalgesia may be used as endpoints, or more objective endpoints, reliant on electrophysiological or imaging technologies (such as functional magnetic resonance imaging) may be employed (Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C. & Buchel, C. (2002) Brain 125, 1326-1336). All such models require evidence of objective validation before it can be concluded that they provide evidence in man of supporting the synergistic actions of a combination that have been observed in animal studies.

For the present invention in humans, a suitable alpha-2-delta ligand:atypical antipsychotic ratio range is selected from between 1:50 to 50:1 parts by weight, 1:50 to 20:1, 1:50 to 10:1, 1:50 to 1:1, 1:20 to 50:1, 1:20 to 20:1, 1:20 to 10:1, 1:20 to 1:1, 1:10 to 50:1, 1:10 to 20:1, 1:10 to 10:1, 1:10 to 1:1, 1:1 to 50:1, 1.1 to 20:1 and 1:1 to 10:1, more suitably 1:10 to 20:1, preferably, 1:1 to 10:1.

Optimal doses of each component for synergy can be determined according to published procedures in animal models. However, in man (even in experimental models of pain) the cost can be very high for studies to determine the entire exposure-response relationship at all therapeutically relevant doses of each component of a combination. It may be necessary, at least initially, to estimate whether effects can be observed that are consistent with synergy at doses that have been extrapolated from those that give optimal synergy in animals. In scaling the doses from animals to man, factors such as relative body weight/body surface area, relative absorption, distribution, metabolism and excretion of each component and relative plasma protein binding need to be considered and, for these reasons, the optimal dose ratio predicted for man (and also for patients) is unlikely to be the same as the dose ratio shown to be optimal in animals. However, the relationship between the two can be understood and calculated by one skilled in the art of animal and human pharmacokinetics. Important in establishing the bridge between animal and human effects are the plasma concentrations obtained for each component used in the animal studies, as these are related to the plasma concentration of each component that would be expected to provide efficacy in man. Pharmacokinetic/ pharmacodynamic modeling (including methods such as isobolograms, interaction index and response surface modelling) and simulations may help to predict synergistic dose ratios in man, particularly where either or both of these components has already been studied in man.

It is important to ascertain whether any concluded synergy observed in animals or man is due solely to pharmacokinetic interactions. For example, inhibition of the metabolism of one compound by another might give a false impression of pharmacodynamic synergy.

Thus, according to a further aspect of the present invention, there is provided a synergistic combination for administration to humans comprising an alpha-2-delta ligand and an atypical antipsychotic or pharmaceutically acceptable salts or solvates thereof, where the dose range of each component corresponds to the absolute ranges observed in a non-human animal model, preferably the rat model, primarily used to identify a synergistic interaction.

Suitably, the dose of alpha-2-delta ligand for use in a human is in a range selected from 1-1200mg, 1-500mg, 1-100mg, 1-50mg, 1-25mg, 500-1200mg, 100-1200mg, 100-500mg, 50-1200mg, 50-500mg, or 50-100mg, suitably 50-100mg, b.i.d. or t.i.d., suitably t.i.d., and the dose of atypical antipsychotic is in a range selected from 1-200mg, 1-100mg, 0.25-25mg, 1-50mg, 1-25mg, 10-100mg, 10-50mg or 10-25 mg, suitably 10-100mg, b.i.d or t.i.d, suitably t.i.d.

It will be apparent to the skilled reader that the plasma concentration ranges of the alpha-2-delta ligand and atypical antipsychotic combinations of the present invention required to provide a therapeutic effect depend on the species to be treated, and components used. For example, for gabapentin in the rat, the Cmax values range from 0.520μg/ml to 10.5μg/ml.

It is possible, using standard PK/PD and allometric methods, to extrapolate the plasma concentration values observed in an animal model to predict the values in a different species, particularly human. Thus, as a further aspect of the present invention, there is provided a synergistic combination for administration to humans comprising an alpha-2-delta ligand and an atypical antipsychotic, where the plasma concentration range of each component corresponds to the absolute ranges observed in a non-human animal model, preferably the rat model, primarily used to identify a synergistic interaction. Suitably, the plasma concentration range in the human corresponds to a range of 0.05μg/ml to 10.5μg/ml for an alpha-2-delta ligand in the rat model.

Particularly preferred combinations of the invention include those in which each variable of the combination is selected from the suitable parameters for each variable. Even more preferable combinations of the invention include those where each variable of

the combination is selected from the more suitable, most suitable, preferred or more preferred parameters for each variable.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are prepared by methods well known to those skilled in the art. Specifically, the patents, patent applications and publications, mentioned hereinabove, each of which is hereby incorporated herein by reference, exemplify compounds which can be used in the combinations, pharmaceutical compositions, methods and kits in accord with the present invention, and refer to methods of preparing those compounds.

The compounds of the present combination invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, which may contain isotopic substitutions (e.g. D2O, d6-acetone, d6-DMSO), are equivalent to unsolvated forms and are encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof. Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the invention or a suitable salt or derivative thereof.

A number of the alpha-2-delta ligands of the present invention are amino acids. Since amino acids are amphoteric, pharmacologically compatible salts can be salts of appropriate non-toxic inorganic or organic acids or bases. Suitable acid addition salts are the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate, camsylate, citrate, edisylate, esylate, fumarate, gluceptate, gluconate, glucuronate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, hydrogen phosphate,

isethionate, D- and L-lactate, malate, maleate, malonate, mesylate, methylsulphate, 2-napsylate, nicotinate, nitrate, orotate, palmoate, phosphate, saccharate, stearate, succinate sulphate, D- and L-tartrate, and tosylate salts. Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc, choline, diolamine, olamine, arginine, glycine, tromethamine, benzathine, lysine, meglumine and diethylamine salts. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The compounds of the invention may also be formed as a zwitterion.

A suitable salt for amino acid compounds of the present invention is the hydrochloride salt. For a review on suitable salts see Stahl and Wermuth, Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Wiley-VCH, Weinheim, Germany (2002).

Also within the scope of the invention are clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in non-stoichiometric amounts. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of the invention include references to salts thereof and to solvates and clathrates of compounds of the invention and salts thereof.

Also included within the present scope of the compounds of the invention are polymorphs thereof.

Prodrugs of the above compounds of the invention are included in the scope of the instant invention. The chemically modified drug, or prodrug, should have a different pharmacokinetic profile to the parent, enabling easier absorption across the mucosal epithelium, better salt formulation and/or solubility, improved systemic stability (for an increase in plasma half-life, for example). These chemical modifications may be

(1) Ester or amide derivatives which may be cleaved by, for example, esterases or lipases. For ester derivatives, the ester is derived from the carboxylic acid moiety

of the drug molecule by known means. For amide derivatives, the amide may be derived from the carboxylic acid moiety or the amine moiety of the drug molecule by known means.

(2) Peptides which may be recognized by specific or nonspecific proteinases. A peptide may be coupled to the drug molecule via amide bond formation with the amine or carboxylic acid moiety of the drug molecule by known means.

(3) Derivatives that accumulate at a site of action through membrane selection of a prodrug form or modified prodrug form.

(4) Any combination of 1 to 3.

Aminoacyl-glycolic and -lactic esters are known as prodrugs of amino acids (Wermuth C.G., *Chemistry and Industry*, 1980:433-435). The carbonyl group of the amino acids can be esterified by known means. Prodrugs and soft drugs are known in the art (Palomino E., *Drugs of the Future*, 1990;15(4):361-368). The last two citations are hereby incorporated by reference.

The combination of the present invention is useful for the general treatment of pain, particularly neuropathic pain. Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is exclusively activated by noxious stimuli via peripheral transducing mechanisms (Millan 1999 Prog. Neurobio. 57: 1-164 for an integrative Review). These sensory fibres are known as nociceptors and are characterised by small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred after complex processing in the dorsal horn, either directly or via brain stem relay nuclei to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Intense acute pain and chronic pain may involve the same pathways driven by [illegible] and as such cause to provide a persuasive mechanism and

instead contribute to debilitating symptoms associated with a wide range of disease states. Pain is a feature of many trauma and disease states. When a substantial injury, via disease or trauma, to body tissue occurs the characteristics of nociceptor activation are altered. There is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. This leads to hypersensitivity at the site of damage and in nearby normal tissue. In acute pain these mechanisms can be useful and allow for the repair processes to take place and the hypersensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is normally due to nervous system injury. This injury often leads to maladaptation of the afferent fibres (Woolf & Salter 2000 Science 288: 1765-1768). Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. There are a number of typical pain subtypes: 1) spontaneous pain which may be dull, burning, or stabbing; 2) pain responses to noxious stimuli are exaggerated (hyperalgesia); 3) pain is produced by normally innocuous stimuli (allodynia) (Meyer et al., 1994 Textbook of Pain 13-44). Although patients with back pain, arthritis pain, CNS trauma, or neuropathic pain may have similar symptoms, the underlying mechanisms are different and, therefore, may require different treatment strategies. Therefore pain can be divided into a number of different areas because of differing pathophysiology, these include nociceptive, inflammatory, neuropathic pain etc. It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. Back pain, Cancer pain have both nociceptive and neuropathic components.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and sensitise the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994 Textbook of Pain 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmitted rapidly and are responsible for the sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey the dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to pain from strains/sprains,

post-operative pain (pain following any type of surgical procedure), posttraumatic pain, burns, myocardial infarction, acute pancreatitis, and renal colic. Also cancer related acute pain syndromes commonly due to therapeutic interactions such as chemotherapy toxicity, immunotherapy, hormonal therapy and radiotherapy. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to, cancer pain which may be tumour related pain, (e.g. bone pain, headache and facial pain, viscera pain) or associated with cancer therapy (e.g. postchemotherapy syndromes, chronic postsurgical pain syndromes, post radiation syndromes), back pain which may be due to herniated or ruptured intervertabral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament

Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (IASP definition). Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include but are not limited to, Diabetic neuropathy, Post herpetic neuralgia, Back pain, Cancer neuropathy, HIV neuropathy, Phantom limb pain, Carpal Tunnel Syndrome, chronic alcoholism, hypothyroidism, trigeminal neuralgia, uremia, or vitamin deficiencies. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patients quality of life (Woolf and Mannion 1999 Lancet 353: 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd 1999 Pain Supp. 6: S141-S147; Woolf and Mannion 1999 Lancet 353: 1959-1964). They include spontaneous pain, which can be continuous, or paroxysmal and abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events activated in response to tissue injury or the presence of foreign substances, which result in swelling and pain (Levine and Taiwo 1994: Textbook of Pain 45-56). Arthritic pain makes up the majority of the inflammatory pain population. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of RA is unknown, but

current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson 1994 Textbook of Pain 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder 2002 Ann Pharmacother. 36: 679-686; McCarthy et al., 1994 Textbook of Pain 387-395). Most patients with OA seek medical attention because of pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Other types of inflammatory pain include but are not limited to inflammatory bowel diseases (IBD),

Other types of pain include but are not limited to;

-Musculo-skeletal disorders including but not limited to myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, Glycogenolysis, polymyositis, pyomyositis.

-Central pain or 'thalamic pain' as defined by pain caused by lesion or dysfunction of the nervous system including but not limited to central post-stroke pain, multiple sclerosis, spinal cord injury, Parkinson's disease and epilepsy.

-Heart and vascular pain including but not limited to angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma, scleredoma, skeletal muscle ischemia.

-Visceral pain, and gastrointestinal disorders. The viscera encompasses the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders include the functional bowel disorders (FBD) and the inflammatory bowel diseases (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including – for FBD, gastro-esophageal reflux, dyspepsia, the irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and – for IBD, Crohn's disease, ileitis, and ulcerative colitis, which all regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis.

-Head pain including but not limited to migraine, migraine with aura, migraine without aura cluster headache, tension-type headache.

-Orofacial pain including but not limited to dental pain, temporomandibular myofascial pain.

As a yet further aspect, there is provided the use of an alpha-2-delta ligand and an atypical antipsychotic in the manufacture of a medicament for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain.

As an alternative feature, the invention provides the use of a synergistic effective amount of an alpha-2-delta ligand and an atypical antipsychotic in the manufacture of a medicament for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain.

As an alternative aspect, there is provided a method for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain, comprising simultaneous, sequential or separate administration of a therapeutically effective amount of an alpha-2-delta ligand and an atypical antipsychotic, to a mammal in need of said treatment.

As an alternative feature, there is provided a method for the curative, prophylactic or palliative treatment of pain, particularly neuropathic pain, comprising simultaneous, sequential or separate administration of a therapeutically synergistic amount of an alpha-2-delta ligand and an atypical antipsychotic, to a mammal in need of said treatment.

The biological activity of the alpha-2-delta ligands of the invention may be measured in a radioligand binding assay using [^{3}H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue (Gee N.S., Brown J.P., Dissanayake V.U.K., Offord J., Thurlow R., Woodruff G.N., *J. Biol. Chem.*, 1996;271:5879-5776). Results may be expressed in terms of μM or nM α2δ binding affinity.

The ability of compounds of the invention to act as atypical antipsychotics can be measured according to established procedures, particularly those described in the documents mentioned hereinabove.

The elements of the combination of the instant invention may be administered separately, simultaneously or sequentially for the treatment of pain. The combination may also optionally be administered with one or more other pharmacologically active agents. Suitable optional agents include:

(i) opioid analgesics, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine and pentazocine;

(ii) nonsteroidal antiinflammatory drugs (NSAIDs), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen,ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, and their pharmaceutically acceptable salts;

(iii) barbiturate sedatives, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal, thiopental and their pharmaceutically acceptable salts;

(iv) benzodiazepines having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam and their pharmaceutically acceptable salts,

(v) H_1 antagonists having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine, chlorcyclizine and their pharmaceutically acceptable salts;

(vi) miscellaneous sedatives such as glutethimide, meprobamate, methaqualone, dichloralphenazone and their pharmaceutically acceptable salts;

(vii) skeletal muscle relaxants, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, orphrenadine and their pharmaceutically acceptable salts,

(viii) NMDA receptor antagonists, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2- piperidinecarboxylic acid and their pharmaceutically acceptable salts;

(ix) alpha-adrenergic active compounds, e.g. doxazosin, tamsulosin, clonidine and 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

(x) tricyclic antidepressants, e.g. desipramine, imipramine, amytriptiline and nortriptiline;

(xi) anticonvulsants, e.g. carbamazepine and valproate;

(xii) Tachykinin (NK) antagonists, particularly Nk-3, NK-2 and NK-1 e.g. antagonists, (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant and 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S,3S)

(xiii) Muscarinic antagonists, e.g oxybutin, tolterodine, propiverine, tropsium chloride and darifenacin;

(xiv) COX-2 inhibitors, e.g. celecoxib, rofecoxib and valdecoxib;

(xv) Non-selective COX inhibitors (preferably with GI protection), e.g. nitroflurbiprofen (HCT-1026);

(xvi) coal-tar analgesics, in particular, paracetamol;

(xvii) neuroleptics, such as droperidol;

(xviii) Vanilloid receptor agonists, e.g. resinferatoxin;

(xix) Beta-adrenergic compounds such as propranolol;

(xx) Local anaesthetics, such as mexiletine;

(xxi) Corticosteriods, such as dexamethasone

(xxii) serotonin receptor agonists and antagonists;

(xxiii) cholinergic (nicotinic) analgesics;

(xxiv) miscellaneous agents such as Tramadol®;

(xxv) PDEV inhibitors, such as sildenafil, vardenafil or taladafil;

(xxvi) serotonin reuptake inhibitors, e.g. fluoxetine, paroxetine, citalopram and sertraline;

(xxvii) mixed serotonin-noradrenaline reuptake inhibitors, e.g. milnacipran, venlafaxine and duloxetine;

(xxviii) noradrenaline reuptake inhibitors, e.g. reboxetine.

The present invention extends to a product comprising an alpha-2-delta ligand, an atypical antipsychotic and one or more other therapeutic agents, such as those listed above, for simultaneous, separate or sequential use in the curative, prophylactic treatment of pain, particularly neuropathic pain.

The combination of the invention can be administered alone but one or both elements will generally be administered in an admixture with suitable pharmaceutical excipient(s), diluent(s) or carrier(s) selected with regard to the intended route of administration and standard pharmaceutical practice. If appropriate, auxiliaries can be added. Auxiliaries are preservatives, anti-oxidants, flavours or colourants. The compounds of the invention may be of immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release type.

The elements of the combination of the present invention can be administered, for example but not limited to, the following route: orally, buccally or sublingually in the form of tablets, capsules, multi-and nano-particulates, gels, films (incl. muco-adhesive), powder, ovules, elixirs, lozenges (incl. liquid-filled), chews, solutions, suspensions and sprays. The compounds of the invention may also be administered as osmotic dosage form, or in the form of a high energy dispersion or as coated particles or fast-dissolving, fast -disintegrating dosage form as described in Ashley Publications, 2001 by Liang and Chen. The compounds of the invention may be administered as crystalline or amorphous products, freeze dried or spray dried. Suitable formulations of the compounds of the invention may be in hydrophilic or hydrophobic matrix, ion-exchange resin complex, coated or uncoated form and other types as described in US 6,106,864 as desired.

Such pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), mannitol, disintegrants such as sodium starch glycolate, crosscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), triglycerides, hydroxypropylcellulose (HPC), bentonite sucrose, sorbitol, gelatin and acacia. Additionally, lubricating agents may be added to solid compositions such as magnesium stearate, stearic acid, glyceryl behenate,

PEG and talc or wetting agents, such as sodium lauryl sulphate. Additionally, polymers such as carbohydrates, phospoholipids and proteins may be included.

Fast dispersing or dissolving dosage fromulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol or xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used, i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared.

The solid dosage form, such as tablets are manufactured by a standard process, for example, direct compression or a wet, dry or melt granulation, melt congealing and extrusion process. The tablet cores which may be mono or multi-layer may be coated with appropriate overcoats known in the art.

Solid compositions of a similar type may also be employed as fillers in capsules such as gelatin, starch or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. Liquid compositions may be employed as fillers in soft or hard capsules such as gelatin capsule. For aqueous and oily suspensions, solutions, syrups and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol, methylcellulose, alginic acid or sodium alginate, glycerin, oils, hydrocolloid agents and combinations thereof. Moreover, formulations containing these compounds and excipients may be presented as a dry product for constitution with water or other suitable vehicles before use.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

The elements of the combination of the present invention can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, intraduodenally, or intraperitoneally, intraarterially, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intraspinally or subcutaneously, or they may be administered by infusion, needle-free injectors or implant injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution, suspension or emulsion (or system so that can include micelles) which may contain other substances known in the art, for example, enough salts or carbohydrates such as glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. For some forms of parenteral administration they may be used in the form of a sterile non-aqueous system such as fixed oils, including mono- or diglycerides, and fatty acids, including oleic acid. The preparation of suitable parenteral formulations under sterile conditions for example lyophilisation is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle (e.g. sterile, pyrogen-free water) before use.

Also, the elements of the combination of the present invention can be administered intranasally or by inhalation. They are conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist) or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA

227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubron (trade mark) or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol (optionally, aqueous ethanol) or a suitable agent for dispersing, solubilising or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules, blisters and cartridges (made, for example, from gelatin or HPMC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol or magnesium stearate.

Prior to use in a dry powder formulation or suspension formulation for inhalation the elements of the combination of the invention will be micronised to a size suitable for delivery by inhalation (typically considered as less than 5 microns). Micronisation could be achieved by a range of methods, for example spiral jet milling, fluid bed jet milling, use of supercritical fluid crystallisation or by spray drying.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1 to 100μl. A typical formulation may comprise the elements of the combination of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents may be used in place of propylene glycol, for example glycerol or polyethylene glycol.

Alternatively, the elements of the combination of the invention may be administered topically to the skin, mucosa, dermally or transdermally, for example, in the form of a gel, hydrogel, lotion, solution, cream, ointment, dusting powder, dressing, foam, film, skin patch, wafers, implant, sponges, fibres, bandage, microemulsions and combinations thereof. For such applications, the compounds of the invention can be suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, fixed oils, including synthetic mono- or

diglycerides, and fatty acids, including oleic acid, water, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, alcohols such as ethanol. Alternatively, penetration enhancers may be used. The following may also be used; polymers, carbohydrates, proteins, phospolipids in the form of nanoparticles (such as niosomes or liposomes) or suspended or dissolved. In addition, they may be delivered using iontophoresis, electroporation, phonophoresis and sonophoresis.

Alternatively, the elements of the combination of the invention can be administered rectally, for example in the form of a suppository or pessary. They may also be administered by vaginal route. For example, these compositions may be prepared by mixing the drug with suitable non-irritant excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the cavity to release the drug.

The elements of the combination of the invention may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline. A polymer may be added such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer (e.g. hydroxypropylmethylcellulose, hydroxyethylcellulose, methyl cellulose), or a heteropolysaccharide polymer (e.g. gelan gum). Alternatively, they may be formulated in an ointment such as petrolatum or mineral oil, incorporated into bio-degradable (e.g. absorbable gel sponges, collagen) or non-biodegradable (e.g. silicone) implants, wafers, drops, lenses or delivered via particulate or vesicular systems such as niosomes or liposomes. Formulations may be optionally combined with a preservative, such as benzalkonium chloride. In addition, they may be delivered using iontophoresis. They may also be administered in the ear, using for example but not limited to the drops.

The elements of the combination of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, taste-masking, bioavailability and/or stability property of a

drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

The term 'administered' includes delivery by viral or non-viral techniques. Viral delivery mechanisms include but are not limited to adenoviral vectors, adeno- associated viral (AAV) vectors, herpes viral vectors, retroviral vectors, lentiviral vectors, and baculoviral vectors. Non-viral delivery mechanisms include lipid mediated transfection, lipsomes, immunoliposomes, lipofectin, cationic facial amphiphiles (CFAs) and combinations thereof. The routes for such delivery mechanisms include but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical or sublingual routes.

Thus, as a further aspect of the present invention, there is provided a pharmaceutical composition comprising a combination comprising an alpha-2-delta ligand, an atypical antipsychotic, or pharmaceutically acceptable salts thereof, and a suitable excipient, diluent or carrier. Suitably, the composition is suitable for use in the treatment of pain, particularly neuropathic pain.

As an alternative aspect of the present invention, there is provided a pharmaceutical composition comprising a synergistic combination comprising an alpha-2-delta ligand, an atypical antipsychotic, or pharmaceutically acceptable salts thereof, and a suitable excipient, diluent or carrier. Suitably, the composition is suitable for use in the treatment of pain, particularly neuropathic pain.

For non-human animal administration, the term 'pharmaceutical' as used herein may be replaced by 'veterinary.'

The element of the pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets,

capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active components. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compounds being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compounds. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

For veterinary use, a combination according to the present invention or veterinarily acceptable salts or solvates thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

BIOLOGY EXAMPLES

METHODS

Animals

Male Sprague Dawley rats (200-250g), obtained from Charles River, (Margate, Kent, U.K.) are housed in groups of 6. All animals are kept under a 12h light/dark cycle (lights on at 07h 00min) with food and water *ad libitum*. All experiments are carried out by an observer unaware of drug treatments.

CCI surgery in the rat

Animals are anaesthetised with isoflurane. The sciatic nerve is ligated as previously described by Bennett and Xie, 1988. Animals are placed on a homeothermic blanket for the duration of the procedure. After surgical preparation the common sciatic nerve is exposed at the middle of the thigh by blunt dissection through biceps femoris. Proximal to the sciatic trifurcation, about 7mm of nerve is freed of adhering tissue and 4 ligatures (4-0 silk) are tied loosely around it with about 1mm spacing. The incision is closed in layers and the wound treated with topical antibiotics.

Effect of combinations on the maintenance of CCI-induced static and dynamic allodynia

Dose-responses to gabapentin and an atypical antipsychotic are first performed alone in the CCI model. Combinations are examined following a fixed ratio design. A dose-response to each fixed dose ratio of the combination is performed. On each test day, baseline paw withdrawal thresholds (PWT) to von Frey hairs and paw withdrawal latencies (PWL) to a cotton bud stimulus are determined prior to drug treatment.

Evaluation of allodynia

Static allodynia is measured using Semmes-Weinstein von Frey hairs (Stoelting, Illinois, U.S.A.). Animals are placed into wire mesh bottom cages allowing access to the underside of their paws. Animals are habituated to this environment prior to the start of the experiment. Static allodynia is tested by touching the plantar surface of the animals right hind paw with von Frey hairs in ascending order of force (0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29g) for up to 6sec. Once a withdrawal response is established, the paw is re-tested, starting with the next descending von Frey hair until no response occurs. The highest force required to lift the paw as well as elicit a response, thus represents the cut off point. The lowest amount of force required to elicit a response is recorded as the PWT in grams.

Dynamic allodynia is assessed by lightly stroking the plantar surface of the hind paw with a cotton bud. Care is taken to perform this procedure in fully habituated rats that are not active to avoid recording general motor activity. At least three measurements are taken at each time point the mean of which represents the paw withdrawal latency (PWL).

If no reaction is exhibited within 15s the procedure is terminated and animals are assigned this withdrawal time. Thus 15s effectively represents no withdrawal. A withdrawal response is often accompanied with repeated flinching or licking of the paw. Dynamic allodynia is considered to be present if animals responded to the cotton stimulus before 8s of stroking.

Combination studies

Dose responses are first performed to both the alpha-2-delta ligand (p.o.) and atypical antipsychotic (s.c. or p.o.) alone. A number of fixed dose ratios of the combination may then be examined. Dose responses to each fixed dose ratio are performed with the time-course for each experiment determined by the duration of antiallodynic-action of each separate ratio. Various fixed dose ratios of the combinations by weight may be examined.

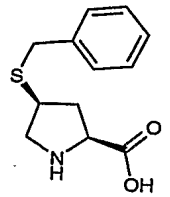
Suitable atypical antipsychotic compounds of the present invention may be prepared as described in the references or are obvious to those skilled in the art on the basis of these documents.

Suitable alpha-2-delta ligand compounds of the present invention may be prepared as described herein below or in the aforementioned patent literature references, which are illustrated by the following non-limiting examples and intermediates.

The following examples and preparations illustrate the preparation of alpha-2-delta ligands disclosed in PCT/IB03/04697:

EXAMPLE 1

(2*S*,4*S*)-4-(Benzylsulfanyl)-pyrrolidine-2-carboxylic acid



To a solution of (2S, 4S)-4-benzylsulfanyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (Preparation 2, 130mg, 3.3mmol) in dichloromethane (2.5ml) was added

trifluoroacetic acid (2.5ml) and the mixture stirred at room temperature under a nitrogen atmosphere for 36 hours. The solvent was removed under reduced pressure and the residue purified by ion-exchange chromatography using Dowex™ 50WX8-200 resin eluting first with water and then with 10% aq ammonia to give the title compound (66mg, 75%) as a white solid.

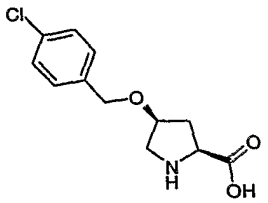
^{1}H-NMR (400MHz, D_2O) δ = 1.88-1.98 (1H, m); 2.45-2.56 (1H, m); 3.07-3.13 (1H, m); 3.22-3.38 (2H, m); 3.66-3.74 (2H, s); 3.93-4.01 (1H, m); 7.11-7.29 (5H, m)

LRMS (electrospray) : m/z [MH^+] 238; [MNa+] 260; [MH^-] 236

Microanalysis : Found C, 59.36; H, 6.33; N, 5.77. $C_{12}H_{15}NO_2S$. 0.3 H_2O requires C, 59.38; H, 6.48; N, 5.77

EXAMPLE 2

(2*S*,4*S*)-4-[(4-Chlorobenzyl)oxy]-pyrrolidine-2-carboxylic acid



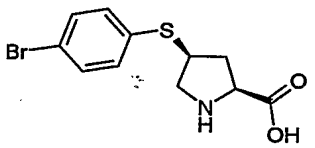
(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-[(4-chlorobenzyl)oxy]-2-pyrrolidinecarboxylic acid (Preparation 4, 96mg, 0.38mmol) was dissolved in dichloromethane (5ml). Trifluoroacetic acid (5ml) was added and the mixture left overnight at room temperature. The reaction mixture was partitioned between dichloromethane (25ml) and water (25ml). The aqueous layer was separated, washed with more dichloromethane (25ml) and evaporated to dryness. The product was purified using Dowex™ 50WX8-200 resin, eluting first with water then 9:1 water:ammonia yielding the title compound (5mg, 5% yield) as a white solid.

^{1}H-NMR (400MHz, CD_3OD) δ = 2.4-2.5(m, 1H), 2.6-2.7(m, 1H), 3.4-3.5(m, 1H), 3.6-3.7(m, 1H), 4.5-4.7(m, 4H), 7.3-7.5(m, 4H).

LCMS (electrospray): m/z [M] 254

EXAMPLE 3

(2*S*,4*S*)-4-[(4-Bromobenzyl)oxy]- pyrrolidine-2-carboxylic acid



(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (Preparation 7, 54mg, 0.14mmol) was dissolved in 4M HCl in dioxan and stirred for 2h at rt. The solvent was removed in vacuo to give a cream solid (32mg, 76%).

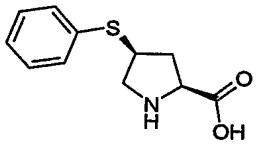
^{1}H-NMR (400MHz, CD_3OD) δ = 2.20 (1H, m), 2.83 (1H, m), 3.32 (1H, m), 3.70 (1H, m), 4.15 (1H, m), 4.50 (1H, m), 7.40 (2H, d), 7.55 (2H, m).

LRMS (electrospray) : m/z [MH^+] 302, 304.

Microanalysis : Found C, 39.01; H, 4.23; N, 4.14. $C_{11}H_{12}NO_2SBr$. 0.9 HCl requires C, 39.44; H, 3.88; N, 4.18.

EXAMPLE 4

(2*S*,4*S*)-4-phenylthio-pyrrolidine-2-carboxylic acid



The title compound was made by the method of Example 3 starting from the title compound of Preparation 8. The yield was 60% and the title compound was a white solid.

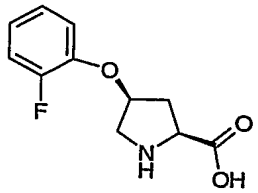
^{1}H-NMR (400MHz, CD_3OD) δ = 2.19 (1H, m), 2.80 (1H, m), 3.34 (1H, m), 3.70 (1H, m), 4.10 (1H, m), 4.56 (1H, m), 7.030-7.60 (5H, m).

LCMS (Electrospray): m/z [MH^+] 224.

Microanalysis : Found C, 48.95; H, 5.50; N, 4.97. $C_{11}H_{13}NO_2S$. HCl. 0.5H_2O requires C, 49.16; H, 5.63; N, 5.21.

EXAMPLE 5

(2*S*,4*S*)-4-[2-Fluorophenoxy]-pyrrolidine-2-carboxylic acid



The title compound was made by the method of Example 3 in 74% yield starting from the title compound from preparation 10.

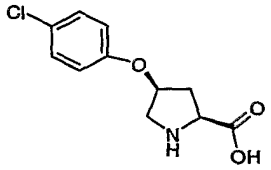
^{1}H-NMR (400MHz, MeOD): δ= 2.60 – 2.76 (m, 2H), 3.57 – 3.65 (m, 1H), 3.75 (d, 2H), 4.56 – 4.64 (m, 1H), 4.85 (s, 3H), 5.18 – 5.24 (m, 1H), 6.98 – 7.19 (m, 4H).

LRMS (electrospray): [M-1] 224, [MH$^+$] 226.

Microanalysis: Found: C, 50.38; H, 4.95; N, 5.29% $C_{11}H_{12}FNO_3$ requires C,50.49; H, 5.01, N, 5.35%

EXAMPLE 6

(2*S*,4*S*)-4-[(4-Chlorophenoxy]-pyrrolidine-2-carboxylic acid



The BOC protected product (250mg, 0.73mmol) from Preparation 12 was stirred in 4M HCl in dioxan (5ml) at 0° C for 2 hours. Diethylether (10ml) was added and the resultant precipitate filtered off and washed with diethylether to give the title compound (178mg, 87%).

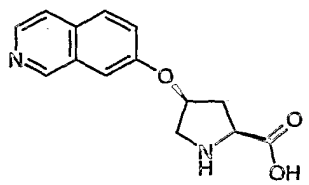
^{1}H-NMR (400 MHz, MeOD): δ =2.59 –2.71 (m, 2H), 3.56 – 3.72 (m, 2H), 4.57 – 4.66(m, 1H) , 4.82 – 4.93 (M, 3H), 5.17 – 5.25 (m, 1H), 6.88 – 6.98 (m, 2H), 7.26 – 7.36 (m, 2H).

LRMS (Electrospray): [M-1] 240, [MH$^+$] 242, [MNa$^+$] 264.

Microanalysis: Found: C, 47.48; H, 4.71; N, 4.92. $C_{11}H_{12}ClNO_3$.HCl requires C, 47.50; H, 4.71; N, 5.04%

EXAMPLE 7

(2*S*,4*S*)-4-[2-Isoquinolinoxy]-pyrrolidine-2-carboxylic acid



(2S, 4S)-4-(Isoquinolin-7-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butylester (Preparation 13, 120mg, 0.29mmol) was stirred in TFA (3ml) for 4.5 hours at room temperature. The solvent was removed in vacuo and triturated with diethyl ether to give an extremely hygroscopic solid which was redissolved in 2I HCl (3ml) and stirred at room temperature for one hour. The solution was washed once with diethylether (5ml)

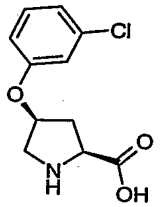
and the aqueous evaporated to give a foam. Trituration with ether gave the title compound as a glass (24mg, 28%).

^{1}H-NMR (400 MHz, CH_3OD): δ =2.68-2.80(m, 1H), 2.82 – 2.97 (m, 1H), 3.75 – 3.91 (m, 2H), 4.62 – 4.75 (m, 1H), 4.75 – 4.96 (m, 5H exchangeable), 5.48 – 5.60 (m, 1H), 7.75 – 7.81 (m, 1H), 7.98 – 8.02 (m, 1H), 8.26 (d, 1H), 8.39 – 8.55 (m, 2H), 9.64 (s, 1H)

LRMS (Electrospray) [M-1] 257, [MH^+] 259

EXAMPLE 8

(2S, 4S)-4-(3-Chloro-phenoxy)-pyrrolidine-2-carboxylic acid



A solution of preparation 15 (29.25mol) was dissolved in THF (20L) & filtered. To this solution was added 4M HCl in dioxane (30L) & stirred overnight. Tert-Butyl methyl ether (70L) was added to the resultant suspension & the product was collected by filtration (7.06kg, 86.7%).

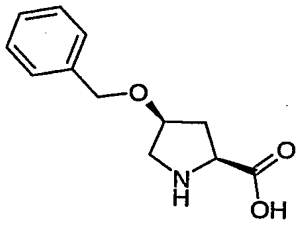
^{1}H NMR (400 MHz, CD_3OD): δ = 2.65 (m, 2H), 3.60 (dd, 1H), 3.70 (d, 1H), 4.60 (dd, 1H), 5.02 (m, 1H), 6.88 (m, 1H), 6.97 (s, 1H), 7.03 (d, 1H), 7.29 (dd, 1H).

LRMS (Electrospray [MH^+] 242, [M-1] 240.

Microanalysis: Found, C, 46.97; H, 4.70; N, 4.90. $C_{11}H_{12}ClNO_3.HCl.0.1H_2O$ requires C, 47.20; H, 4.75; N, 5.00.

EXAMPLE 9

(2*S*,4*S*)-4-(Benzyloxy)-pyrrolidine-2-carboxylic acid



(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(benzyloxy)-pyrrolidine-2-carboxylic acid (Preparation 17, 150mg, 0.47mmol) was dissolved in dichloromethane (5ml). Trifluoroacetic acid (5ml) was added and the mixture left stirring overnight at room

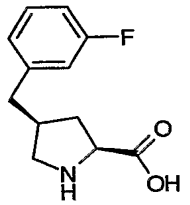
temperature. The reaction mixture was partitioned between dichloromethane (25ml) and water (25ml). The aqueous layer was separated, washed with more dichloromethane (25ml) and evaporated to dryness. The product was purified using an ion exchange column (Dowex 50WX8-200 resin), eluting first with water then 9:1 water:ammonia yielding the title compound (34mg, 33% yield) as a white solid.

^{1}H-NMR (400MHz, CD_3OD) δ = 2.3-2.5 (m, 1H), 3.1-3.18 (m, 1H), 3.4-3.5 (d, 1H), 3.9-3.95(m, 1H), 4.2 (s, 1H), 4.4-4.55 (dd, 3H), 7.2-7.4 (m, 5H).

LCMS (Electrospray): m/z [MNa^+] 244.

EXAMPLE 10

(2*S*,4*S*)-4-(3-Fluoro-benzyl)-pyrrolidine-2-carboxylic acid mono hydrochloride salt



4-(3-Fluoro-benzyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-(2-isopropyl-5-methyl-cyclohexyl) ester (Preparation 35, 0.91 g, 1.96 mmol) was dissolved in toluene (2 ml). 6N hydrochloric acid (50ml) was added and stirred at reflux for 18 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 20 ml). The aqueous layer was concentrated by evaporated under reduced pressure to give the title compound (417mg, 81 %) as a white solid. ^{1}H-NMR showed a 7:1 ratio of *cis:trans* diastereoisomers so the product was recrystallised from isopropyl alcohol to give the title compound (170mg, 65%) in a ratio of 14:1 *cis:trans* as determined by NMR.

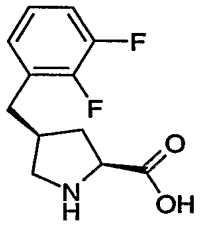
^{1}H-NMR (400MHz, CD_3OD): (mixture of diastereoisomers 2*S*,4*S*:2*S*,4*R* *(14:1)*): δ = 1.85 (q, 1H), 2.51 (quin, 1H), 2.69-2.85 (m, 3H), 3.07 (t, 1H), 3.41 (dd, 1H), 4.38 and 4.48 (t, 1H), 6.90-7.04 (m, 3H), 7.32 (q, 1H).

LRMS (APCI): m/z [$MH]^+$ 224.

$[\alpha]_D^{25}$ –1.27° (c=9.00 in methanol).

Microanalysis: Found C, 55.56; H, 5.81; N, 5.34%. $C_{12}H_{14}FNO_2.HCl$ requires C, 55.50; H, 5.82; N, 5.39%.

(2*S*,4*S*)-4-(2,3-Difluoro-benzyl)-pyrrolidine-2-carboxylic acid mono-hydrochloride salt



The title compound was made from by the method of Example 10, starting from the title compound of Preparation 37, and purified by re-crystallisation with acetone/ether to give the title compound as a mixture of diastereoisomers (2*S*,4*S*:2*S*,4*R* (12:1)) determined by ^{1}H-NMR (500 mg, 60 %) as a white solid.

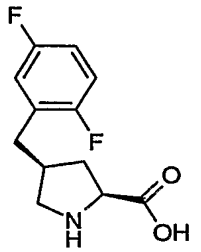
^{1}H-NMR (400 MHz, CD_3OD) (mixture of diastereoisomers *cis* :*trans (12:1)*): δ= 0.80-1.90 (m, 0.92H), 2.12-2.20 (m, 0.08H), 2.28-2.36 (m, 0.08H), 2.49-2.58 (q, 0.92H), 2.66-2.81 (m, 1H), 2.83-2.95 (m, 2H), 3.02-3.13 (t, 1H), 3.46 (dd, 1H), 4.40 (dd, 0.92H), 4.48-4.54 (m, 0.08H), 7.03-7.20 (m, 3H).

LRMS (Electrospray): m/z $[M + H]^+$ 242.

Microanalysis: Found C, 51.42; H, 5.08; N, 5.01%. $C_{12}H_{13}NO_2F_2.HCl$ requires C, 51.90; H, 5.08; N, 5.04%.

EXAMPLE 12

(2*S*,4*S*)-4-(2,5-Difluoro-benzyl)-pyrrolidine-2-carboxylic acid mono hydrochloride salt



The title compound was made by the method of Example 10, starting from the title compound of Preparation 36.

^{1}H-NMR (400MHz, CD_3OD): (mixture of diastereoisomers 2*S*,4*S*:2*S*,4*R (26:1)*): δ = 1.86 (q, 1H), 2.51-2.54 (m, 1H), 2.75-2.83 (m, 3H), 3.09 (t, 1H), 3.45 (q, 1H), 4.39 and 4.49 (2t, 1H) 26:1, 7.00-7.14 (m, 3H).

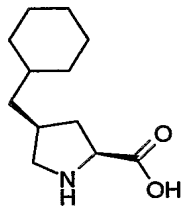
LRMS (APCI): m/z $[MH]^+$ 242.

Microanalysis: Found C, 50.18; H, 4.94; N, 4.83%. $C_{12}H_{13}F_2NO_2$.HCl requires C, 51.90; H, 5.08; N, 5.04%.

$[\alpha]_D^{25}$ –0.22° (c=1.84 in methanol).

EXAMPLE 13

(2*S*,4*S*)-4-Cyclohexylmethyl-pyrrolidine-2-carboxylic acid mono hydrochloride salt



4-Cyclohexylmethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-(2-isopropyl-5-methyl-cyclohexyl) ester (Preparation 38, 316 mg, 0.70 mmol) was dissolved in toluene (2 ml). 6N hydrochloric acid (50ml) was added and stirred at reflux for 72 hours. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 20 ml). The aqueous layer was concentrated by evaporation under reduced pressure to give the title compound as a white solid (80mg, 48%).

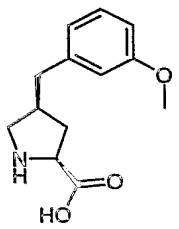
^{1}H-NMR (400MHz, CD_3OD): (mixture of diastereoisomers 2*S*,4*S*:2*S*,4*R* *(6:1)*): δ = 0.83-1.00 (m, 2H), 1.13-1.40 (m, 6H), 1.62-1.81 (m, 6H), 2.48 (m, 2H), 2.90 (t, 1H), 3.48 (t, 1H), 4.32 and 4.42 (2t, 1H).

LRMS (APCI): m/z $[MH]^+$ 212.

$[\alpha]_D^{25}$ –1.86° (c=2.04 in methanol).

EXAMPLE 14

(2*S*,4*S*)-4-(3-Methoxy-benzyl)-pyrrolidine-2-carboxylic acid mono hydrochloride salt



The title product was made by the method of Example 10, starting from the title compound of Preparation 39.

^{1}H-NMR (400MHz, CD_3OD): (mixture of diastereoisomers 2*S*,4*S*:2*S*,4*R* *(15:1)*): δ = 1.79-1.89 (m, 1H), 2.47-2.52 (m, 1H), 2.68-2.77 (m, 3H), 3.06 (t, 1H), 3.36 (t, 1H), 3.39 (s, 3H), 4.37 and 4.47 (t, 1H), 6.81 (d, 3H), 7.22 (t, 1H).

LRMS (APCI): m/z $[MH]^+$ 236.

Microanalysis: Found C, 56.77; H, 6.62; N, 5.06%. $C_{13}H_{17}NO_3$.HCl requires C, 57.46; H, 6.68; N, 5.15%.

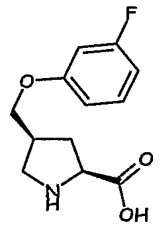
$[\alpha]_D^{25}$ –6.90° (c=3.1, MeOH).

EXAMPLE 14A

(2*S*,4*S*)-4-(3-Methoxy-benzyl)-pyrrolidine-2-carboxylic acid mono hydrochloride salt may also be prepared by the method of J. Ezquerra, C. Pedegrel, B. Yrurtagoyena and A. Rubio in *J. Org. Chem.* 1995, 60, 2925-2930.

EXAMPLE 15

(2*S*,4*S*)-4-(3-Fluoro-phenoxymethyl)-pyrrolidine-2-carboxylic acid



4-(3-Fluoro-phenoxymethyl)-pyrroline-1,2-dicarboxylic acid di-tert-butyl ester (Preparation 44, 475mg, 1.2mmol) was dissolved in a solution of anhydrous hydrogen chloride in dioxane (4M, 15ml) and stirred at 50°C under a nitrogen atmosphere for 1 hour. The solvent was removed under reduced pressure and the resulting semi-solid triturated with ethyl acetate to give a white solid which was recrystallised from ethyl acetate/isopropyl alcohol to give the title compound as a mixture of diastereomers (~5:1 2*S*,4*S*:2*S*,4*R*) as a white solid hydrochloride salt (90mg, 35%)

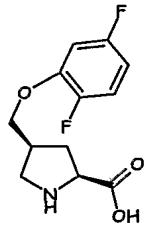
^{1}H-NMR (400MHz, CD_3OD): δ = 2.04-2.09 (m, 0.8H); 2.33-2.47 (m, 0.4H); 2.65-2.75 (m, 0.8H); 2.88-3.00 (m, 1H); 3.33-3.40 (m, 1H); 3.52-3.60 (m, 0.8H); 3.60-3.68 (0.2H); 3.96-4.04 (m, 1H); 4.04-4.12 (m, 1H); 4.42-4.51 (m, 0.8H); 4.40-4.56 (m, 0.2H); 6.65-6.80 (m, 3H), 7.21-7.30 (m, 1H)

LRMS (electrospray): [M+1] 240; [M+23] 262; [M-1] 238.

The following compounds may be prepared by a method analogous to that of Example 15:

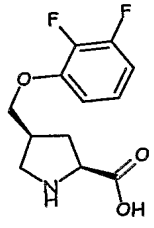
EXAMPLE 16

(2*S*,4*S*)-4-(2,5-Difluoro-phenoxymethyl)-pyrrolidine-2-carboxylic acid;



EXAMPLE 17

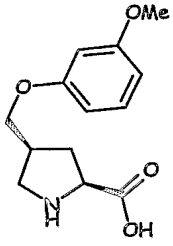
(2*S*,4*S*)-4-(2,3-Difluoro-phenoxymethyl)-pyrrolidine-2-carboxylic acid;



and

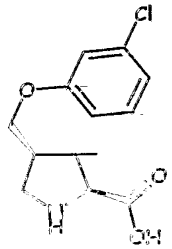
EXAMPLE 18

(2*S*,4*S*)-4-(3-Methoxy- phenoxymethyl)-pyrrolidine-2-carboxylic acid



EXAMPLE 19

(2*S*,4*S*)-4-(3-Chloro-phenoxymethyl)-pyrrolidine-2-carboxylic acid



(2*S*,4*S*)-4-(3-Chloro-phenoxymethyl)-pyrrolidine-1,2-dicarboxylic acid di-*tert*-butyl ester [illegible]

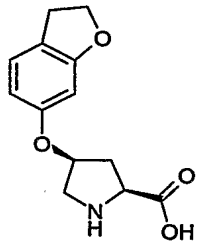
chloride in dioxane (4M, 5ml) and stirred for 18 hours at room temperature. The solvent was removed under reduced pressure and the residue triturated with ethyl acetate to give the title compound as a white solid hydrochloride salt (13mg, 27%)

^{1}H-NMR (400MHz, CD_3OD): δ = 2.07-2.18 (m, 1H); 2.63-2.74 (m, 1H); 2.88-3.00 (m, 1H); 3.32-3.40 (m, 1H); 3.52-3.61 (m, 1H); 3.96-4.04 (m, 1H); 4.04-4.10 (m, 1H); 4.42-4.51 (t, 1H); 6.82-6.89 (d, 1H); 6.80-7.00 (m, 2H); 7.20-7.28 (t, 1H)

LRMS (electrospray): [M+1] 256; [M+23] 278; [M-1] 254

EXAMPLE 20

(2*S*,4*S*)-4-(2,3-Dihydro-benzofuran-6-yloxy)-pyrrolidine-2-carboxylic acid



The title compound was made by the method of Example 3 in 100% yield as a pale yellow solid.

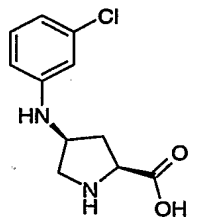
^{1}H-NMR (400 MHz, D_2O): δ = 2.35 – 2.56 (m, 2H); 2.86 – 3.04 (m, 2H); 3.35 – 3.65 (m, 2H); 4.10 –4.26 (m, 3H); 4.97 - 5.05 (m, 1 H); 6.20 - 6.36 (m, 2H); 7.02 (d, 1H).

LRMS (electrospray): [MH^+] 250

Microanalysis: Found : C54,16; H, 5.78; N, 4.72%. $C_{13}H_{15}NO_4$.HCl. 0.15H_2O requires C,54.14; H,5.70; N,4.86.

EXAMPLE 21

(2*S*,4*S*)-4-(3-Chloro-phenylamino)-pyrrolidine-2-carboxylic acid



4-(3-Chloro-phenylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (Preparation 41, 155mg, 0.456mmol)was stirred in 4 M HCl in dioxan (4ml) at 0°C for 2 hours. Ether (4ml) was added and the resultant white hygroscopic solid filtered off and dried in vacuo at 40°C to give the title compound (90mg, 60.3%).

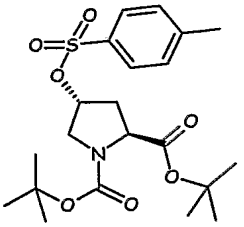
^{1}H-NMR (400 MHz, CD_3OD): 2.20 – 2.29(m, 1H); 2.95 – 3.05 (m, 1H); 3.28 – 3.39 (m, 2H); 4.22 – 4.31 (m, 1H); 4.45 – 4.55 (m, 1H); 4.90 (s, 5H); 6.62 (d, 1H); 6.70 – 6.75 (m, 2H); 7.13 (t, 1H).

LRMS (electrospray): [M-1] 239.

Microanalysis : Found: C,40.37; H,5.07; N,8.46%. $C_{11}H_{13}ClN_2O_2.2HCl.\ 0.75\ H_2O$ requires C,40.39; H,5.08; N,8.56.

Preparation 1

(2S, 4R)-4-(Toluene-4-sulfonyloxy)-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester



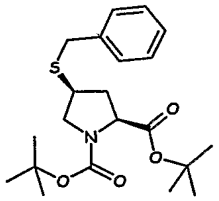
To a solution of (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (CAS Reg. No. 170850-75-6) (1g, 3.48mmol) in 20ml of CH_2Cl_2 was added pyridine (3.9ml) and *p*-toluene sulphonyl chloride (0.7g, 3.67mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 72 hours. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (100ml) and washed with saturated citric acid solution (50ml) then water (50ml). The organic phase was dried (magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate:heptane (3:10) to give the title compound (1.5g, 98%) as a colourless gum.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.39-1.49 (18H, m), 2.01-2.16 (1H, m), 2.33-2.6 (4H, m), 3.50-3.64 (2H, m), 4.20-4.29 (1H, m), 4.96-5.06 (1H, m); 7.31-7.40 (2H, m), 7.65-7.80 (2H, m).

LRMS (electrospray) : m/z [MH^+] 464, [MH^-] 440

Preparation 2

(2S, 4S)-4-Benzylsulfanyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester



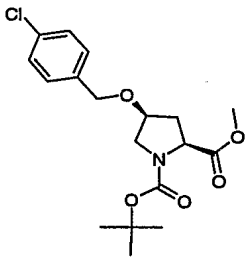
To a solution of Preparation 1 (200mg, 4.53mmol) in ethanol (10ml) under a nitrogen atmosphere was added benzyl mercaptan (0.107ml, 8.86mmol) and potassium tert-butoxide (101mg, 8.86mmol) and the mixture stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (25ml) and was washed with water (10ml). The organic phase was dried (magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified by column chromatography eluting with heptane:ethyl acetate (9:1) to give the title compound (130mg, 73%) as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.38-1.50 (18H, m), 1.80-1.90 (1H, m), 2.44-2.55 (1H, m), 3.00-3.29 (2H, m), 3.70-3.78 (2H, s), 3.84-3.95 (1H, m), 4.04-4.16 (1H, m), 7.27-7.34 (5H, m).

LRMS (electrospray) : m/z [MNa^+] 416

Preparation 3

(2S,4S)-4-(4-Chloro-benzyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



(2S, 4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyester (CAS Reg. No. 227935-38-8)(300mg, 1.0mmol) and 60% sodium hydride mineral oil dispersion (61mg, 1.1mmol) were dissolved in anhydrous dimethylformamide (9ml) at 0°C under a nitrogen atmosphere. After 10mins stirring 4-chlorobenzylbromide (265mg, 1.2mmol) in CH_2Cl_2 (1ml) was added drop wise and the reaction mixture stirred to room temperature for 1 hour. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (25ml), washed with water (2 x 25ml), dried (magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified using

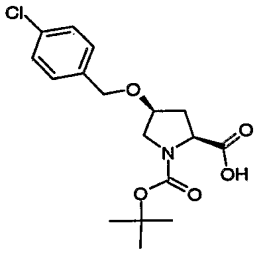
flash chromatography eluting with a solvent gradient 4:1 heptane:ethyl acetate, yielding the title compound (170mg, 40% yield) as an oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.4-1.5(m, 9H), 2.0-2.45(m, 2H), 3.5-3.8(m, 5H), 4.05-4.2(s, 1H), 4.25-4.4(m, 1H), 4.4-4.55(m, 2H), 7.3(m, 4H).

LCMS (Electrospray): m/z [MNa^+] 392.

Preparation 4

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-[(4-chlorobenzyl)oxy]-pyrrolidine-2-carboxylic acid



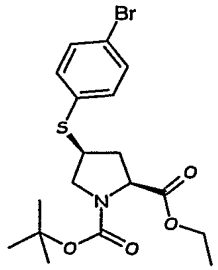
The title compound from Preparation 3 (157mg, 0.42mmol) was dissolved in tetrahydrofuran (10ml). $LiOH.H_2O$ (54mg, 1.3mmol) was dissolved in water (5ml). The two solutions were mixed, left stirring at room temperature for two days then evaporated to dryness under reduced pressure. The remaining residue was dissolved in ethyl acetate (25ml) and washed with saturated citric acid (25ml). The organic fraction was dried (magnesium sulphate), filtered and evaporated to dryness under reduced pressure. The residue was purified using flash chromatography eluting with a solvent gradient of 20:1 dichloromethane:methanol, yielding the title compound (106mg, 71% yield) as an oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.4(m, 9H), 2.9-3.0(m, 1H), 3.4-3.6(m, 2H), 4.2-4.7(m, 5H), 7.2-7.35(m, 4H).

LCMS (Electrospray): m/z [M^+] 354

Preparation 5

(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester



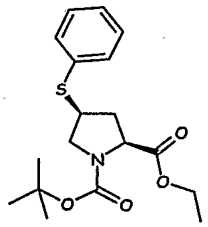
Sodium ethoxide (112mg, 1.65mmol) was added slowly to a stirred solution of 4-bromothiophenol (302mg, 1.65mmol) in EtOH (6ml) at room temperature under a nitrogen atmosphere. A solution of (2S, 4R)-4-(toluene-4-sulfonyloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg. No. 88043-21-4) (300mg, 0.75mmol) in 1ml EtOH was added after 30 minutes and the solution was stirred for 48h. The reaction mixture was poured into 0.5M NaOH (50ml) and extracted with CH_2Cl_2 (2 x 50ml). The combined organics were dried (magnesium sulphate) and concentrated under vacuum. Flash column chromatography yielded the product as a pink solid (120mg, 40%).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.25 (3H, t), 1.40 (9H, s), 2.00 (1H, s), 2.60 (1H, m), 3.35 (1H, m), 3.60 (1H, m), 3.90 (1H, s), 4.18 (2H, q), 4.22 (1H, m), 7.35 (2H, d), 7.40 (2H, d).

LRMS (Electrospray) : m/z [MNa^+] 454.

Preparation 6

(2S, 4S)-4-(Phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester



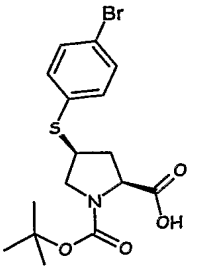
The title compound was made by the method of Preparation 5 in 40% yield as a pink solid.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.23 (3H, t), 1.41 (9H, s), 2.00 (1H, m), 2.61 (1H, m), 3.38 (1H, m), 3.62 (1H, m), 3.90-4.03 (1H, m), 4.15-4.35 (3H, m), 7.20-7.50 (5H, m).

LRMS (Electrospray) : m/z [MNa^+] 374.

Preparation 7

(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



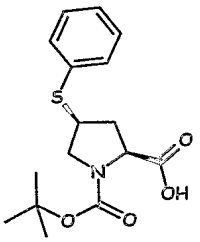
(2S, 4S)-4-(4-Bromo-phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (Preparation 5, 120mg, 0.30mmol) was dissolved in MeOH (6ml) and 2M sodium hydroxide was added (0.83ml, 1.66mmol). The solution was stirred for 14h, concentrated and added to 0.5M HCl (50ml). The aqueous was extracted with CH_2Cl_2 (50ml) which was dried (magnesium sulphate) and concentrated. Flash column chromatography (eluting first with CH_2Cl_2 and then with 95% CH_2Cl_2 / MeOH) gave the acid as a clear liquid (130mg, 48%).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.43 (9H, s), 2.4-2.8 (2H, m), 3.35 (1H, m), 3.62 (1H, m), 3.8-4.0 (1H, m), 4.3-4.4 (1H, m), 7.28 (2H, m), 7.41 (2H, m).

LRMS (Electrospray) : m/z [M^-] 400, 402.

Preparation 8

(2S, 4S)-4-(Phenylsulfanyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



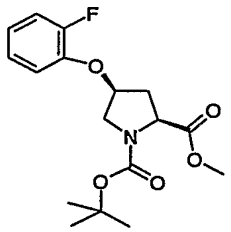
The title compound was made by the method of Preparation 7 from the title compound of Preparation 6 in 83% yield as a clear oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.41 (9H, s), 2.10 (0.5H, m), 2.38 (0.5H, m), 2.50-2.75 (1H, m), 3.36 (1H, m), 3.62 (1H, m), 3.82-4.03 (1H, m), 4.25-4.41 (1H, m), 7.20-7.45 (5H, m).

LRMS (Electrospray) : m/z [M^-] 322.

Preparation 9

4-(2-Fluoro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



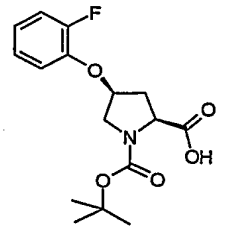
(2S, 4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg. No. 74844-91-0) (300mg, 1.22mmol) was dissolved in THF (10 ml), and triphenylphosphine (385mg, 1.47mmol) and 2-fluorophenol (164.5mg, 1.47mmol) were added. The reaction was cooled in ice, DIAD (0.23ml, 1.2mmol) added dropwise and the reaction stirred at room temperature overnight. The mixture was concentrated in vacuo, CH_2Cl_2 (20ml) added and the solution washed with 2N NaOH (10ml). The phases were separated and the organic phase washed with saturated brine (10ml), dried over $MgSO_4$ and evaporated. The residue was dissolved in a minimum of diethylether and pentane added until solution just maintained. After seeding with triphenylphosphine oxide, the solution was cooled in ice and the resultant precipitate filtered. The filtrate was evaporated and the residue purified by flash chromatography on silica (50g) eluting initially with pentane:diethylether (2:1 by volume), then pentane:diethylether (1:1 by volume) to give the title product (388mg, 58%) as an impure oil containing diisopropylbicarbamate as an impurity.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.45 (d,9H), 2.35 – 2.57 (m, 2H),3.65 –3.79 (m, 5H), 4.43 – 4.57 (m, 1H), 4.88 – 5.02 (m, 1H), 6.81 – 6.98 (m, 2H), 6.98 – 7.10 (m, 2H).

LRMS (Electrospray): m/z [MNa^+] 362

Preparation 10

(2S, 4S)-4-(2-Fluoro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



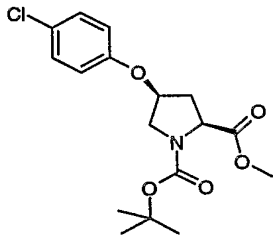
The ester (400mg, 1.18mmol) from Preparation 9 was dissolved in THF (4 ml) and $LiOH.H_2O$ (106mg, 3.53mmol) in water (2ml) was added. The mixture was stirred at room temperature overnight. After washing with CH_2Cl_2 (10ml), the aqueous solution was adjusted to pH 2 with saturated aqueous citric acid and re-extracted with CH_2Cl_2 (2 x 10ml). The combined organic extracts were backwashed with saturated brine, dried over $MgSO_4$, filtered and evaporated to give the title compound as a white solid (383mg, 49%) containing a small impurity of diisopropylbicarbamate (2%) by NMR.

^{1}H-NMR (400 MHz, $CDCl_3$): δ =1.16-1.70 (m, 9H), 2.20-2.92 (m, 2H), 3.58-3.85 (m, 2H), 4.38-4.63 (m, 1H), 4.83-5.02 (m, 1H), 6.78-7.17 (m, 4H).

LRMS (Electrospray) : m/z [M-1] 324

Preparation 11

(2S, 4S)-4-(4-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



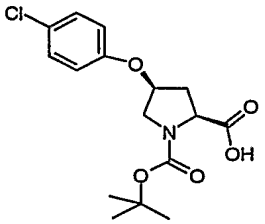
(2S, 4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg. No. 74844-91-0) (1.10g, 4.08mmol) was dissolved in THF (25ml) and 4-chlorophenol (0.78g, 6.12mmol) and triphenylphosphine (1.6g, 6.12mmol) were added. The solution was cooled in and ice bath and DIAD (0.96ml, 4.88mmol) added dropwise. The reaction was stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in diethylether (20ml) and pentane added until solution was only just maintained. The solution was seeded with triphenylphosphine oxide and cooled in ice. The resultant precipitate was filtered and the filtrate evaporated. The residue was purified by flash chromatography on silica (100g), loading with pentane : diethylether (2:1 by volume) and eluting with pentane : diethylether (1 : 1 by volume) to give the title compound as a colourless oil (1.35g, 69%) containing a small impurity of diisopropylbicarbamate (CAS Reg. No. 19740-72-8) by NMR.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.43 (d, 9H), 2.36-2.57 (m, 2H), 3.61-3.81 (m, 5H), 4.38-4.59 (m, 1H), 4.60-4.80 (m, 1H), 6.84-6.92 (m, 2H), 7.16-7.30 (m, 2H).

LRMS (Electrospray): m/z [MNa^+] 378

Preparation 12

(2S, 4S)-4-(4-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



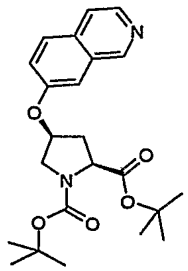
The ester from Preparation 11 was dissolved in THF (30ml) and a solution of $LiOH.H_2O$ (440mg, 10.56mmol) in water (15ml) was added. The reaction was stirred at room temperature overnight, and then the solvent concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20ml) and saturated aqueous citric acid solution (10ml) and the phases separated. The organic layer was washed with saturated brine (10ml), dried over $MgSO_4$, and evaporated. The crude product was partially purified by flash chromatography on silica (100g) eluting initially with CH_2Cl_2 and then CH_2Cl_2 : MeOH (25 : 1 by volume) to give material which still contained diisopropylbicarbamate by NMR. Recrystallisation from EtOAc yielded white crystals which were filtered and washed with EtOAc: pentane (1 :1) to give the title compound (517mg, 55%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.23-1.67 (m, 9H), 2.20-2.88 (m, 2H), 3.55-3.81 (m, 2H), 4,40-4.61 (m, 1H), 4.78-4.92 (m, 1H), 6.63-6.84 (m, 2H), 7.11-7.32 (m, 2H)

LRMS (Electrospray) : m/z [M-1] 340

Preparation 13

(2S, 4S)-4-(Isoquinolin-7-yloxy)-pyrrolidine-1,2-dicarboxylicacid di-tert-butyl ester



The title compound was synthesised from (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (CAS Reg. No. 170850-75-6) and isoquinolin-7-ol

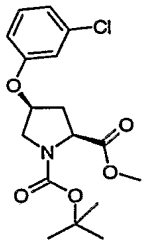
using the same method as preparation 11 and gave the title compound as an oil in 15% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.41-1.53 (m, 18H), 2.43-2.63 (m, 2H), 3.68-3.97 (m, 2H), 4.30-4.52 (m, 1H), 4.99-5.06 (m, 1H), 7.08 -7.16 (m, 1H), 7.41-7.77 (m,, 3H), 8.42 (d, 1H), 9.10-9.18 (m, 1H).

LCMS (Electrospray): m/z [MH^+] 415

Preparation 14

(2S, 4S)-4-(3-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



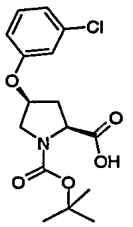
To a stirred solution of (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg 74844-91-0) (6.1kg,24.87mol), 3-chlorophenol (3.52kg,27.39mol) & triphenylphosphine (7.18kg,27.37mol) in tert-butyl methyl ether (30.5L) at 0'C was added diisopropylazodicarboxylate (5.53kg,27.35mol) in tert-butyl methyl ether (15L) dropwise. The mixture was stirred overnight at 20'C. The reaction was filtered and the liquors washed with 0.5M sodium hydroxide (aq) (2 x 12.5L) & water (12.2L). The tert-butyl methyl ether solvent was replaced with n-heptane (42.7L) by atmospheric pressure distillation & cooled to crystallise crude product, which was collected by filtration (11.1kg, 125% contaminated with ca 35% reduced diisopropyl dicarboxylate & triphenylphosphine oxide - corrected yield = 86%).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.46, 1.49 (2 x s, 9H), 2.47 (2H, m), 3.71 (5H, m), 4.42 (1H, m), 4.42, 4.54 (1H, 2 x m), 4.87 (1H, m), 6.68 (1H, m), 6.79 (1H, s), 6.92 (1H, m), 7.18 (1H, m).

LRMS (Electrospray): m/z 378 (MNa^+).

Preparation 15

(2S, 4S)-4-(3-Chloro-phenoxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



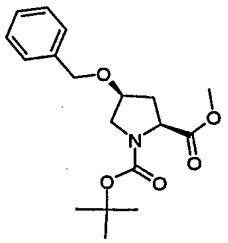
To the products of preparation 14 (11.1kg, 20.28mol) in THF (26.6L) was added a solution of $LiOH.H_2O$ (4.86kg, 115.4mol) in water (55.5L). The mixture was stirred overnight at 25'C. The THF was removed by distillation & the resultant aqueous solution extracted with dichloromethane (33.3L & 16.7L). The combined dichloromethane layers were extracted with water (33L & 16.7L). The combined aqueous phases were adjusted to pH 3-3.5 with 1M hydrochloric acid(aq) & extracted with dichloromethane (2 x 22.2L). The combined dichloromethane phases were replaced with toluene (33.3L), which was cooled to crystallise the product, which was collected by filtration (6.1kg, 98%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.42, 1.48 (2 x s, 9H), 2.30-2.70 (m, 2H), 3.60-3.80 (m, 2H), 4.40-4.60 (m, 1H), 4.86 (m, 1H), 6.71 (m, 1H), 6.82 (m, 1H), 6.94 (m, 1H), 7.16 (m, 1H).

LRMS (Electrospray): m/z [MNa^+] 364, 340 [M-1] 340.

Preparation 16

(2S,4S)-4-Benzyloxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



(2S, 4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (CAS Reg. No. 227935-38-8)(300mg, 1.2mmol) and 60% sodium hydride mineral oil dispersion (61mg, 1.5mmol) were dissolved in anhydrous dimethylformamide (9ml) at 0°C under a nitrogen atmosphere. After 10mins stirring benzylbromide (0.153ml, 1.3mmol) in CH_2Cl_2 (1ml) was added drop wise and the reaction mixture stirred to room temperature for 1 hour. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (25ml), washed with water (2 x 25ml), dried (magnesium

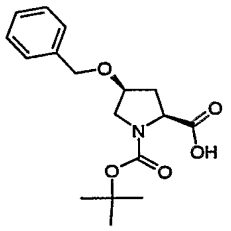
sulphate), filtered and evaporated under reduced pressure. The residue was purified using flash chromatography eluting with a solvent gradient 4:1 heptane:ethyl acetate, yielding the title compound (167mg, 42% yield) as an oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.2-1.6(m, 12H), 2.2-2.45(m, 1H), 3.4-3.8 (m, 4H), 4.05-4.2 (m, 1H), 4.3-4.5 (m, 2H), 7.15-7.4 (m, 5H).

LCMS (Electrospray): m/z [MNa^+] 358.

Preparation 17

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(benzyloxy)-pyrrolidine-2-carboxylic acid

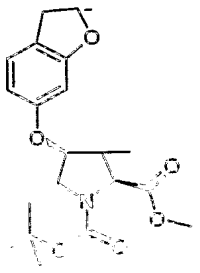


The title compound from Preparation 16 (167mg, 0.5mmol) was dissolved in tetrahydrofuran (10ml). $LiOH.H_2O$ (63mg, 1.5mmol) was dissolved in water (5ml). The two solutions were mixed, left stirring at room temperature for two days then evaporated to dryness under reduced pressure. The remaining residue was dissolved in ethyl acetate (25ml) and washed with saturated citric acid (25ml). The organic fraction was dried (magnesium sulphate), filtered and evaporated to dryness under reduced pressure. The crude compound (150mg, 94% yield) was taken on to the next stage (Example 9) as an oil.

LCMS (Electrospray): m/z [M^-] 320, [MNa^+] 344.

Preparation 18

(2*S*,4*S*)-4-(2,3-Dihydro-benzofuran-6-yloxy)-pyrrolidine-1,2-dicarboxylic acid-1-tert-butyl ester 2-methyl ester



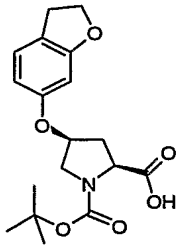
The title compound was prepared from (2S, 4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl-ester 2-methyl ester and 2,3-dihydro-benzofuran-6-ol by the method of Preparation 14 in 41.6% yield as a white solid.

^{1}H- NMR (400MHz, $CDCl_3$): δ = 1.43 (d, 9H); 2.36 – 2.50 (m, 2H); 3.03 –3.17 (m, 2H); 3.59 – 3.80 (m, 5H); 4.15 – 4.41 (m, 3H); 4.78 – 4.83 (m, 1H); 6.21 – 6.32 (m, 2H); 6.98 – 7.02 M, 1H).

LRMS (electrospray): [MNa^+] 386

Preparation 19

(2*S*,4*S*)-4-(2,3-Dihydro-benzofuran-6-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



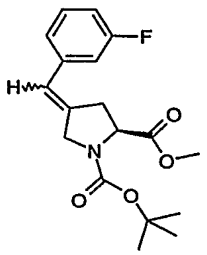
The title compound was made from 4-(2,3-dihydro-benzofuran-6-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester by the method of Preparation 15 in 78% yield as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.38 – 1.58 (m, 9H); 2.21 – 2.83(m, 2H); 3.02 – 3.18 (m, 2H); 3.59 – 3.82 (m, 2H); 4.38 – 4.60 (m, 3H); 4.80 – 4.90 (m, 1H); 6.22 – 6.42 (m, 2H); 6.97 – 7.10 (m, 1H).

LRMS (electrospray): [M-1] 348

Preparation 20.

4-(3-Fluoro-benzylidene)-pyrrolidine-1,2-dicarboxylic acid-1-tert butyl ester 2-methyl ester



To a solution of *m*-fluorobenzyl triphenylphosphonium[2] bromide (8.08 g, 0.018 mmol) in anhydrous dichloromethane (200 ml), was added potassium *t*-butoxide (1M in THF, 17.2 ml, 0.017 mmol) dropwise at room temperature and stirred for 1 h. The mixture was cooled to 0°C and to this a solution of the (2S) 4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert butyl ester 2-methyl ester[3] (3.8 g, 0.016 mmol) in dichloromethane (20 ml) was added dropwise. The mixture was warmed to room temperature and stirred for 18 hours. The reaction was quenched with saturated ammonium chloride (100 ml), the aqueous extracted with dichloromethane (2 x 100 ml) and the combined organics dried over magnesium residue was purified by flash chromatography on silica gel eluting with a solvent gradient of heptane:ethyl acetate (4:1) to give the title compound (3.48 g, 67 %) as a colourless oil.

^{1}H-NMR (400 MHz, CD_3OD) (mixture of geometric isomers, *cis* and *trans*): δ = 1.44 (s, 10H), 1.50 (s, 8H), 2.79-2.94 (m, 2H), 3.20-3.37 (m, 2H), 3.66 (d, 3H), 3.72 (d, 3H), 4.20-4.38 (m, 4H), 4.42-4.48 (m, 1H), 4.52-4.60 (m, 1H), 6.42-6.51 (m, 2H), 6.89-7.10 (m, 6H), 7.30-7.40 (m, 2H).

LRMS (APCI): m/z $[(M+H) -Boc]^+$ 236.

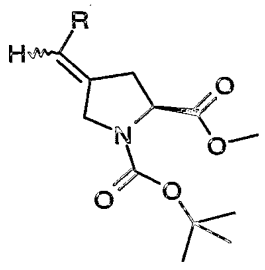
Microanalysis: Found: C, 64.46; H, 6.77; N, 4.07%. $C_{18}H_{22}FNO_4$. requires C, 64.46; H, 6.61; N, 4.18%.

2. K. Rafizadeh and K.Yates; *J.Org. Chem.* **1984**, 49, 9, 1500-1506.

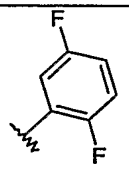
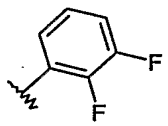
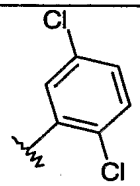
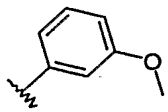
3. *Org. Lett*, **2001**, 3041-3043.

Preparations 21 -24.

The compounds of the following tabulated examples of the general formula:

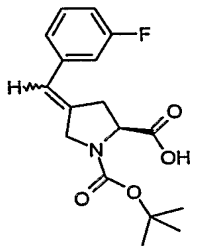


were prepared by a method analogous to that of Preparation 20 using the appropriate phosphonium bromide salt and (2S) 4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert butyl ester 2-methyl ester[3]

Prep. no.	R	LRMS (APCI) m/z =[ ]$^+$	Analytical data
21		354 [MH]	^{1}H-NMR (400MHz, CD_3OD): (mixture of geometric isomers *cis* and *trans*)δ = 1.45 (d, 9H), 2.78-2.88 (m, 1H), 3.20-3.32 (m, 1H), 3.70 (d, 3H), 4.15-4.31 (m, 2H), 4.50 (dt, 1H), 6.51 (s, 1H), 6.98-7.13 (m, 3H).
22		254 [(M-H)-Boc]	Microanalysis: Found: C, 61.25; H, 6.16; N, 3.89%. $C_{18}H_{21}F_2NO_4$. requires C, 61.18; H, 5.99; N, 3.96%; $[\alpha]_D^{25}$ -5.52° (c = 2.68 in methanol)
23		286 [M-Boc]	^{1}H-NMR (400 MHz, CD_3OD) (mixture of geometric isomers, *cis* and *trans*): δ = 1.44 (2 x s, 5H), 1.50 (2 x s, 4H), 2.70-2.92 (m, 1H), 3.20-3.40 (m, 1H), 3.69 (d, 1.5H), 3.72 (d, 1.5H), 4.08-4.20 (m, 0.5H), 4.23-4.29 (m, 1.5H), 4.44-4.59 (m, 0.5H), 4.51-4.57 (m, 0.5H), 6.55-6.64 (brm, 1H), 7.23-7.30 (m, 1.5H), 7.34 (d, 0.5H), 7.37-7.42 (m, 1H). Microanalysis: Found: C, 56.63; H, 5.74; N, 3.58%. $C_{18}H_{21}Cl_2NO_4$. 0.05 heptane. requires C, 56.33; H, 5.62; N, 3.58%; $[\alpha]_D^{25}$ = -8.70° (c = 3.08 in methanol)
24		348 [MH]	^{1}H-NMR (400MHz, CD_3OD): (mixture of geometric isomers, *cis* and *trans*) δ = 1.45 (d, 9H), 2.77-2.91 (m, 1H), 3.23-3.30 (m, 1H), 3.70 (dd (3H), 3.78 (s, 3H), 4.19-4.30 (m, 2H), 4.49 (dt, 1H), 6.42-6.48 (m, 1H), 6.75-6.85 (m, 3H), 7.22-7.28 (m, 1H). Microanalysis: Found C, 68.66; H, 7.48; N, 4.12%. $C_{19}H_{25}NO_5$ requires C, 68.86; H, 7.60; N, 4.23%

Preparation 25.

4-(3-Fluoro-benzylidene)-pyrrolidine-1,2-dicarboxylic acid-1-*tert* butyl ester



To a stirred solution of 4-(3-fluoro-benzylidene)-pyrrolidine-1,2-dicarboxylic acid 1-*tert* butyl ester 2-methyl ester (3.23 g, 9.63 mmol) in tetrahydrofuran (150 ml), was added 1M lithium hydroxide monohydrate (1.21 g, 28.9 mmol) in water (50 ml). The mixture was stirred at room temperature for 3 days. Tetrahydrofuran was removed by evaporation under reduced pressure, the residue diluted with water (30 ml) and acidified to pH 2.0-3.0 using 1M hydrochloric acid. The aqueous was extracted with diethyl ether (3 x 100 ml) and the combined organics dried over magnesium sulfate. The solvent was removed by evaporation under reduced pressure to give the title compound (2.37 g, 77 %) as a white foam.

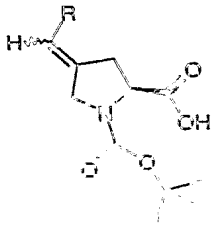
^{1}H-NMR (400 MHz, CD_3OD) (mixture of geometric isomers, *cis* and *trans*): δ = 1.44 (s, 5H), 1.50 (s, 4H), 2.80-2.96 (m, 1H), 3.20-3.38 (m, 1H), 4.24-4.34 (m, 2H), 4.45-4.45 (m, 0.5H), 4.46-4.58 (m, 0.5H), 6.43-6.54 (m, 1H), 6.90-7.05 (m, 3H), 7.30-7.40 (m, 1H).

LRMS (APCI): m/z $[M-H]^+$ 320.

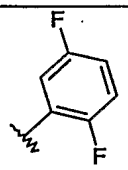
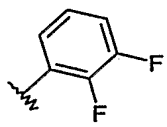
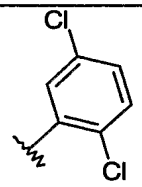
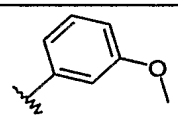
Microanalysis: Found: C, 63.10; H, 6.53; N, 4.05%. $C_{17}H_{20}NO_4F$. requires C, 63.54; H, 6.27; N, 4.36%.

Preparations 26-29.

The compounds of the following tabulated examples of the general formula:

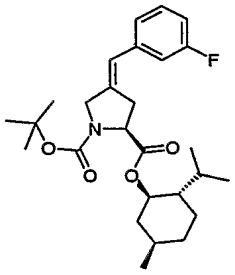


were prepared by a method analogous to that of Preparation 25 using the appropriate starting ester.

Prep. no.	R	LRMS (APCI) m/z = [ ]$^+$	Analytical data
26		677 [2M-H]	^{1}H-NMR (400MHz, CD_3OD): (mixture of geometric isomers, *cis* and *trans*): δ = 1.44 (d, 9H), 2.75-2.92 (m, 1H), 3.18-3.32 (m, 1H), 4.14-4.31 (m, 2H), 4.40-4.55 (m, 1H), 6.53 (s, 1H), 6.95-7.14 (m, 3H).
27		338 [M-H]	^{1}H-NMR (400 MHz, CD_3OD) (mixture of geometric isomers, *cis* and *trans*): δ = 1.42-1.56 (m, 9H), 2.78-2.92 (m, 1H), 3.20-3.36 (m, 1H), 4.05-4.52 (m, 2H), 4.40-4.56 (m, 1H), 6.54-6.60 (brs, 1H), 7.00-7.20 (m, 3H). Microanalysis: Found: C, 59.61; H, 5.80; N, 3.97%. $C_{17}H_{19}F_2NO_4$. requires C, 60.17; H, 5.64; N, 4.13%. $[\alpha]_D^{25}$ -3.64° (c = 2.58 in methanol)
28		370 [M-2H]	^{1}H-NMR (400 MHz, CD_3OD) (mixture of geometric isomers, cis and trans): δ = 1.48 (2 x s, 5H), 1.52 (2 x s, 4H), 2.75-2.80 (m, 0.5H), 2.85-2.95 (m, 0.5H), 3.20-3.33 (m, 1H), 4.10-4.20 (m, 0.5H), 4.24-4.34 (m, 1.5H), 4.40-4.54 (m, 1H), 6.55-6.65 (brs, 1H), 7.24-7.28 (m, 1.5H), 7.38 (d, 0.5H), 7.40 (d, 1H). Microanalysis: Found: C, 54.69; H, 5.29; N, 3.64%. $C_{17}H_{19}Cl_2NO_4$. requires C, 54.85; H, 5.14; N, 3.76%.
29		332 [M-H]	^{1}H-NMR (400MHz, CD_3OD): (mixture of geometric isomers, *cis* and *trans*): δ = 1.44 (d, 9H), 2.79-2.95 (m, 1H), 3.19-3.30 (m, 1H), 3.79 (s, 3H), 4.23-4.39 (m, 2H), 4.40-4.49 (m, 1H), 6.43-6.45 (m, 1H), 6.73-6.84 (m, 3H), 7.22-7.29 (m, 1H).

Preparation 30

4-(3-Fluoro-benzylidene)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-(2-isopropyl-5-methyl-cyclohexyl) ester



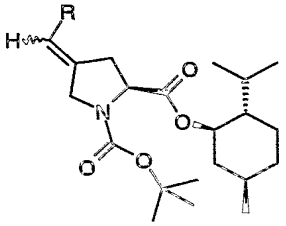
To a solution of 4-(3-fluoro-benzylidene)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (2.68 g, 8.35 mmol), 1R,2S,5R(-) menthol (1.31 g, 8.35 mmol) was added followed by dimethylaminopyridine (1.02 g, 8.35 mmol). The mixture was cooled to 0°C and dicyclohexylcarbodiimide (1.89 g, 9.19 mmol) in dichloromethane (10 ml) was added in one portion. The mixture was warmed to room temperature stirred for 18 h. The mixture was filtered and the filtrate was washed with 1N hydrochloric acid (30 ml), sat. sodium hydrogen carbonate (30 ml) and water (30 ml). The organics were dried over magnesium sulphate and the solvent was removed by evaporation under reduced pressure. Purification by flashmaster column chromatography eluting with heptane:ethyl acetate (12:1) yielded the title compound (1.20 g, 31 %) as a colourless oil.

^{1}H-NMR (400MHz, CD_3OD): δ = 0.55 (t, 2H), 0.69 (t, 2H), 0.80-0.93 (m, 8H), 0.95-1.05 (m, 1H), 1.20-1.35 (m, 2H), 1.44 (d, 9H), 1.60-2.00 (m, 3H), 2.73-2.90 (m, 1H), 4.03-4.68 (m, 4H), 6.43-6.52 (m, 1H), 6.93-7.11 (m, 3H), 7.33-7.40 (m, 1H).

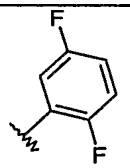
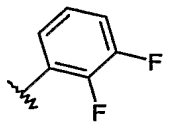
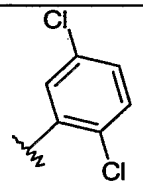
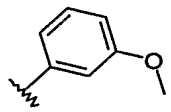
LRMS (APCI): m/z $[MH]^+$ 460.

Preparations 31-34.

The compounds of the following tabulated examples of the general formula:

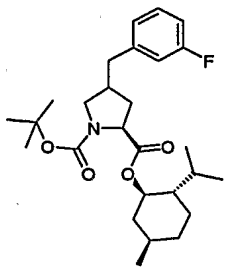


were prepared by a method analogous to that of Preparation 30 using the appropriate starting acid.

Prep. no.	R	LRMS (APCI) m/z =	Analytical data
31		378 [MH-Boc]	Microanalysis: Found C, 67.31; H, 7.88; N, 2.89%. $C_{27}H_{37}F_2NO_2$ requires C, 67.90; H, 7.81; N, 2.93%.
32		478 [MH]	Microanalysis: Found: C, 68.64; H, 8.29; N, 2.7%. $C_{27}H_{37}F_2NO_4$. 0.13heptane requires C, 68.33; H, 8.03; N, 2.85%; $[\alpha]_D^{25}$ -35.57° (c = 3.2 in methanol)
33		510 [MH]	Microanalysis: Found C, 63.75; H, 7.39; N, 2.73%. $C_{27}H_{37}Cl_2NO_4$ requires C, 63.53; H, 7.31; N, 2.74%.
34		372 [MH]	Microanalysis: Found C, 70.60; H, 8.72; N, 2.99%. $C_{28}H_{41}NO_5$ requires C, 71.31; H, 8.76; N, 2.97%. $[\alpha]_D^{25}$ –47.24° (c=1.66, MeOH)

Preparation 35

4-(3-Fluoro-benzyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-(2-isopropyl-5-methyl-cyclohexyl) ester.



4-(3-fluoro-benzylidene)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-(2-isopropyl-5-methyl-cyclohexyl) ester (1.20 g, 2.61 mmol) was dissolved in ethyl acetate:toluene (1:1, 12 ml). The solution was submitted to hydrogenation on platinum oxide (120 mg, 10 % by weight) at 25 °C and 15 psi for 1 hour. The reaction mixture was filtered through arbocel and the filtrate reduced under pressure. The residue was purified

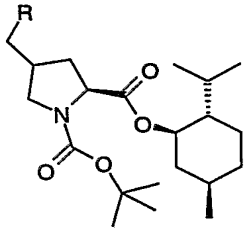
by flashmaster chromatography eluting with heptane:ethyl actetate (15:1) to yield the title compound as a colourless oil (1.11 g, 91 %).

^{1}H-NMR (400MHz, CD_3OD): δ = 0.72-1.37 (m, 13 H), 1.44 (d, 9H), 1.43-1.75 (m, 4H), 1.87-2.01 (m, 2H), 2.31-2.58 (m, 2H), 2.83 (d, 2H), 3.07 (t, 1H), 3.50-3.65 (m, 1H), 4.13-4.30 (dt, 1H), 4.71 (td, 1H), 6.90 (d, 2H), 7.00 (d, 1H), 7.30 (q, 1H).

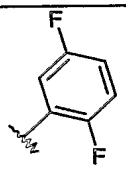
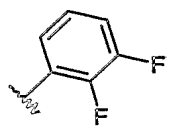
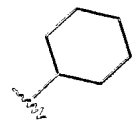
LRMS (APCI): m/z $[MH\text{-}BOC]^+$ 362.

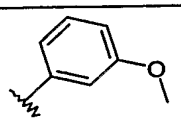
Preparations 36-39.

The compounds of the following tabulated examples of the general formula:



were prepared by a method analogous to that of Preparation 35 using the appropriate starting alkenic menthol ester.

Prep. no.	R	LRMS (APCI) m/z =	Analytical data (mixture of diastereoisomers *cis* (major) and *trans*):
36		380 [MH]	Microanalysis: Found C, 67.22; H, 8.24; N, 2.95%. $C_{27}H_{39}F_2NO_4$ requires C, 67.62; H, 8.20; N, 2.92%.
37		480 [MH]	Microanalysis: Found: C, 67.74; H, 8.30; N, 2.90%. $C_{27}H_{39}F_2NO_4$. requires C, 67.62; H, 8.20; N, 2.92%; $[\alpha]_D^{25}$ -71.92° (c = 3.26 in methanol)
38[i]		350 [MH-Boc]	

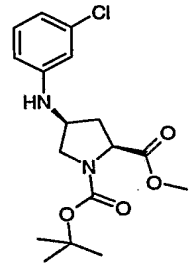
39		374 [MH]	Microanalysis: Found C, 71.02; H, 9.27; N, 2.97%. $C_{28}H_{43}NO_5$ requires C, 71.00; H, 9.15; N, 2.96%. $[\alpha]_D^{25}$ –2.76° (c = 5.3 in methanol)

Footnotes

1. Hydrogenation of the title compound of Preparation 33 was carried out using rhodium on alumina (5 %) (44 mg, 10 % by weight) at 50 °C, 70 psi for 24 h.

Preparation 40

(2*S*,4*S*)-4-(3-Chloro-phenylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester



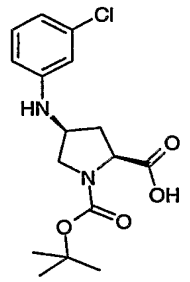
4-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (364.5mg,1.5mmol) and 3-chloroaniline (191mg, 1.5mmol) were dissolved in DCM (10ml). To this solution was added sodium triacetoxyborohydride (413mg, 1.95mmol) and acetic acid (0.085ml, 1.5mmol), and the reaction stirred at room temperature overnight. The reaction mixture was washed with 2N NaOH (5ml), saturated brine (5ml), dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica eluting with DCM to give the title compound as a colourless oil (215mg, 40%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.42 (d, 9H); 2.04-2.17 (m, 1H); 2.39 –2.55 (m, 1H); 3.48 – 3.61 (m, 1H); 3.63 – 3.79(m, 4H); 4.02 –4.15 (m, 1H); 4.25 –4.41 (m, 1H); 6.42 – 6.51 (m, 1H); 6.55 – 6.61 (m, 1H); 6.65 – 6.75 (m, 1H); 7.01 – 7.11 (m, 1H).

LRMS (electrospray): [MNa^+] 377.

Preparation 41

(2*S*,4*S*)-4-(3-Chloro-phenylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



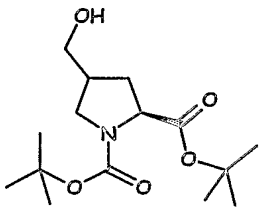
To a solution of the (2*S*,4*S*)-4-(3-chloro-phenylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (200mg, 0.58mmol) in THF (2ml) was added a solution of $LiOH.H_2O$ (73mg 1.74mmol), and the reaction stirred at room temperature overnight. The solvent was concentrated in vacuo and the residual aqueous solution washed with DCM (2ml). The aqueous was then adjusted to pH 5 with saturated aqueous citric acid and re-extracted with DCM (2 x 10ml). These combined extracts were dried over $MgSO_4$ and evaporated to give the title compound as a white foam (168mg, 88%)

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.18 – 1.69 (m, 9H); 2.11 – 2.45 (m, 1H); 2.53 – 2.61 (m, 1H); 3.44 – 3.62 (m, 2H); 4.04 – 4.11 (m, 1H); 4.48 – 4.53 (m, 1H); 6.38 – 6.61 (m, 2H);6.65 – 6.74 (m, 1H); 7.04 – 7.15 (m, 1H).

LRMS (electrospray): [M-1] 339

Preparation 42

4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester



To a solution of 2-methyl-2-butene (2M in tetrahydrofuran, 30ml, 60mmol) in anhydrous tetrahydrofuran (40ml) at 0°C under a nitrogen atmosphere was added borane-tetrahydrofuran complex (1M in tetrahydrofuran, 30ml, 30mmol) dropwise over 10 minutes and allowed to stir for 2 hours. The reaction mixture was cooled to –20°C and a solution of 4-methylene-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (2.84g, 10mmol) (CAS reg 163 190-46-3) in tetrahydrofuran (20ml) was added dropwise and stirred to room temperature over 18 hours. Water (40ml) was added cautiously followed by sodium perborate (3.5g, 30mol), then hydrogen peroxide (27.5% w/w in water, 10ml) [illegible]

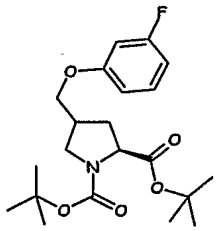
reduced pressure and the aqueous extracted with ethyl acetate (2 x 60ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with 40% ethyl acetate/heptane to give the title compound as a mixture of diastereomers (~5:1 2*S*,4*S*:2*S*,4*R*) as a colourless oil (1.25g, 41%)

^{1}H-NMR (400MHz, CD_3OD): δ = 1.39-1.49 (m, 18H); 1.63-1.75 (m, 0.8H); 1.96-2.07 (m, 0.4H); 2.32-2.47 (m, 1.8H); 3.11-3.20 (m, 1H); 3.46-3.53 (m, 2H); 3.53-3.60 (m, 0.2H); 3.60-3.68 (m, 0.8H); 4.09-4.2 (m, 1H)

LRMS (electrospray): [M+23] 324; [M-1] 300

Preparation 43

4-(3-Fluoro-phenoxymethyl)-pyrroline-1,2-dicarboxylic acid di-tert-butyl ester



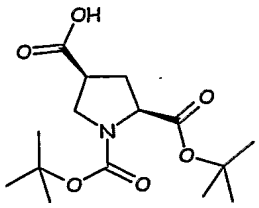
To a solution of 4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (Preparation 42, 500mg, 1.66mmol), triphenylphosphine (653mg, 2.49mmol) and 3-fluorophenol (0.23ml, 2.49mmol) in tetrahydrofuran (30ml) at 0°C under a nitrogen atmosphere was added diisopropylazodicarboxylate (0.49ml, 2.49mmol) dropwise over 5 minutes and stirred to room temperature over 72 hours. Solvent was removed under reduced pressure and the residue purified by chromatography on silica gel, eluting with 10-15% ethyl acetate/heptane to give the title compound as a mixture of diastereomers (~5:1 2*S*,4*S*:2*S*,4*R*) as a colourless oil (370mg, 51%)

^{1}H-NMR (400MHz, CD_3OD): δ = 1.39-1.49 (m, 18H); 1.81-1.95 (m, 0.8H); 2.09-2.20 (m, 0.4H); 2.44-2.59 (m, 0.8H); 2.65-2.80 (m, 1H); 3.22-3.33 (m, 1H); 3.65-3.75 (m, 1H); 3.91-4.00 (m, 1.8H); 4.00-4.07 (m, 0.2H); 4.14-4.26 (m, 1H); 6.60-6.74 (m, 3H); 7.20-7.28 (m, 1H)

LRMS (electrospray): [M+23] 418

Preparation 44

(2*S*,4*S*)-Pyrrolidine-1,2,4-tricarboxylic acid 1,2-di-tert-butyl ester



To a mixture of 4-phenyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (CAS Reg. No. 344 286-69-7)[5] (0.78g, 2.24mmol) and sodium periodate (5.77g, 27mmol) stirring at 0°C under a nitrogen atmosphere in ethyl acetate (5.5ml), acetonitrile (5.5ml) and water (8.5ml) was added ruthenium trichloride (10mg, 0.05mmol) and stirred to room temperature over 18 hours. Diethyl ether (20ml) was added and stirred for a further 1hr. 1M hydrochloric acid (5ml) was added and the mixture extracted with ethyl acetate (3 x 30ml). Organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with 50:50:1 ethyl acetate:heptane:glacial acetic acid to give the title compound as a colourless gum (501mg, 78%)

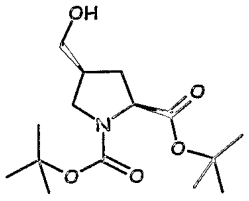
^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.40-1.49 (m, 18H); 2.26-2.40 (m, 1H); 2.42-2.56 (m, 1H); 3.02-3.12 (m, 1H); 3.65-3.80 (m, 1.4H) & 3.80-3.88 (m, 0.6H) [rotamers]; 4.09-4.20 (m, 0.7H) & 4.20-4.26 (m, 0.3H) [rotamers]

LRMS (electrospray): [M-1] 314

5 *J. Org. Chem.*, **2001**, 3593-3596

Preparation 45

(2*S*,4*S*)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester



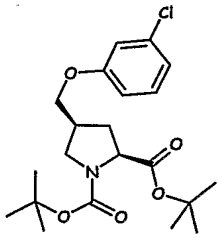
To a solution of pyrrolidine-1,2,4-tricarboxylic acid 1,2-di-tert-butyl ester (Preparation 44, 501mg, 1.59mmol) in anhydrous tetrahydrofuran (10ml) at 0°C under a nitrogen atmosphere was added borane-tetrahydrofuran complex (1M in tetrahydrofuran, 3.16ml, 3.18mmol) dropwise and allowed to stir to room temperature over 18hours. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (10ml) and

and then dried ($MgSO_4$), filtered and evaporated under reduced presssure to give the title compound as a colourless gum (single diastereomer 132mg, 27%)

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.40-1.47 (m, 18H); 1.59-1.80 (m, 1H); 1.80-2.00 (m, 1H); 2.31-2.46 (m, 2H); 3.14-3.21 (m, 1H); 3.54-3.65 (m, 2H); 3.65-3.74 (m, 1H); 4.10-4.20 (m, 1H).

Preparation 46

(2*S*,4*S*)- 4-(3-Chloro-phenoxymethyl)-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester



To a solution of 4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid di-tert-butyl ester (Preparation 45, 132mg, 0.44mmol), triphenylphosphine (172mg, 0.66mmol) and 3-chlorophenol (0.069ml, 0.66mmol) in tetrahydrofuran (5ml) at 0°C under a nitrogen atmosphere was added diisopropylazodicarboxylate (0.129ml; 0.66mmol) dropwise and allowed to stir to room temperature over 18 hours. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel, eluting with 10% ethyl acetate/heptane to give the title compound as a colourless gum (66mg, 37%).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.40-1.56 (m, 18H); 1.80-1.91 (m, 1H); 2.40-2.54 (m, 1H); 2.61-2.70 (m, 1H); 3.24-3.33 (m, 1H); 3.67-3.74 (m, 0.3H) & 3.74-3.81 (m, 0.7H) [rotamers]; 3.84-3.96 (m, 2H); 4.12-4.20 (m, 0.7H) & 4.20-4.26 (m, 0.3H) [rotamers]; 6.67-6.75 (m, 1H); 6.82-6.86 (m, 1H); 6.86-6.93 (m, 1H); 7.10-7.19 (m, 1H)

LRMS (electrospray): [M+23] 434

CLAIMS

1. A combination for the treatment of pain comprising a synergistic amount of an alpha-2-delta ligand and an atypical antipsychotic, or pharmaceutically acceptable salts thereof.

2. A combination according to claim 1 or 2, wherein the alpha-2-delta ligand is selected from gabapentin, pregabalin, [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-Aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-Amino-5-methyl-octanoic acid, or a pharmaceutically acceptable salt thereof.

3. A combination according to claim 1 or 2, wherein the alpha-2-delta ligand is gabapentin.

4. A combination according to claim 1 or 2, wherein the alpha-2-delta ligand is pregabalin.

5. A combination according to any one of claims 1-4 wherein the atypical antipsychotic is selected from ziprasidone, olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, asenapine and amisulpride, or a pharmaceutically acceptable salt thereof.

6. A combination according to any one of claims 1-5 where the atypical antipsychotic is ziprasidone.

7. A pharmaceutical composition for the curative, prophylactic or palliative treatment of pain comprising a therapeutically effective amount of a combination according to any one of claims 1-6, or pharmaceutically acceptable salts thereof and a suitable carrier or excipient.

8. Use of a synergistic effective amount of an alpha-2-delta ligand and an atypical antipsychotic, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the curative, prophylactic or palliative treatment of pain.

9. Use according to claim 8 where the pain is neuropathic pain.

10. A method for the curative, prophylactic or palliative treatment of pain, comprising simultaneous, sequential or separate administration of a therapeutically synergistic amount of an alpha-2-delta ligand and an atypical antipsychotic, or pharmaceutically acceptable salts thereof, to a mammal in need of said treatment.

11. The method according to claim 10 where the pain is neuropathic pain.

ABSTRACT

COMBINATIONS COMPRISING ALPHA-2-DELTA LIGANDS

The instant invention relates to a combination, particularly a synergistic combination, of an alpha-2-delta ligand and an atypical antipsychotic, and pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and their use in the treatment of pain, particularly neuropathic pain.